

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/505, C07D 403/04	A1	(11) International Publication Number: WO 96/40143 (43) International Publication Date: 19 December 1996 (19.12.96)
(21) International Application Number: PCT/US96/10039 (22) International Filing Date: 7 June 1996 (07.06.96) (30) Priority Data: 08/473,396 7 June 1995 (07.06.95) US 08/636,779 19 April 1996 (19.04.96) US (60) Parent Application or Grant (63) Related by Continuation US 08/636,779 (CIP) Filed on 19 April 1996 (19.04.96) (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ADAMS, Jerry, Leroy [US/US]; 611 Forest Road, Wayne, PA 19087 (US). GALLAGHER, Timothy, Francis [US/US]; 255 Manor Road, Harleysville, PA 19438 (US). SISKI, Joseph [US/US]; 180 Logan Drive, Hatfield, PA 19440 (US). PENG, Zhi-Qiang [CN/US]; Apartment A704, 251 West DeKalb Pike,		King of Prussia, PA 19406 (US). OSIFO, Irennegbee, Kelly [US/US]; 309 Conestoga Way, Eagleville, PA 19403 (US). BOEHM, Jeffrey, Charles [US/US]; 248 Anthony Road, King of Prussia, PA 19406 (US). (74) Agents: DINNER, Dana, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). (81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: IMIDAZOLE COMPOUNDS (57) Abstract Novel 1,4,5-substituted imidazole compounds and compositions for use in therapy as cytokine inhibitors.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

Imidazole Compounds

FIELD OF THE INVENTION

- 5 This invention relates to a novel group of imidazole compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION

- 10 Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological
15 activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

- There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid
20 arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to
25 diabetes and pancreatic β cells.

 Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

- Excessive or unregulated TNF production has been implicated in mediating or
30 exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic

shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, 5 cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been 10 identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or 15 maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with 20 monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, 25 have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine 30 production or activity aids in limiting HIV progression as stated above for T-cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

Interleukin-8 (IL-8) is a chemotactic factor first identified and characterized in 1987. IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysachharide (LPS). Human IL-8 has been shown to act on Mouse, Guinea Pig, Rat, and Rabbit Neutrophils. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysosomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophil into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

- 5 This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

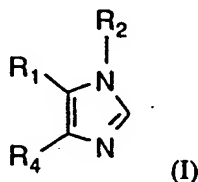
In particular the present invention relates to a method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof.

- 10 This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

- This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).
- 15

This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

Accordingly, the present invention provides a compound of Formula (I):



- R₁ is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is substituted with NHR_a and optionally substituted with an additional, independent, substituent of C₁₋₄ alkyl, halogen, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, N(R₁₀)C(O)R_b or NHR_a;
- 25

R_a is aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclicC₁₋₆ alkyl, heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally substituted;

- R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl;
- R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a
- 5 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, -C(Z)NR₇R₁₇, -C(Z)OR₁₆, -(CR₁₀R₂₀)_vCOR₁₂, -SR₅, -SOR₅, -OR₁₂, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₁₂, -NR₁₀C(Z)R₁₆, or -(CR₁₀R₂₀)_vNR₁₀R₂₀ and which, for other positions of substitution, is halogen, cyano, -C(Z)NR₁₃R₁₄, -C(Z)OR₃, -(CR₁₀R₂₀)_m"COR₃, -S(O)_mR₃, -OR₃, halo-
- 10 substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_m"NR₁₀C(Z)R₃, -NR₁₀S(O)_m"R₈, -NR₁₀S(O)_m"NR₇R₁₇, -ZC(Z)R₃ or -(CR₁₀R₂₀)_m"NR₁₃R₁₄;
- v is 0, or an integer having a value of 1 or 2;
- m is 0, or the integer 1 or 2;
- m' is an integer having a value of 1 or 2,
- 15 m'' is 0, or an integer having a value of 1 to 5;
- R_2 is -(CR₁₀R₂₀)_n' OR₉, heterocyclyl, heterocyclylC₁₋₁₀ alkyl, C₁₋₁₀alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl-C₁₋₁₀-alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroaryl-C₁₋₁₀-alkyl, (CR₁₀R₂₀)_nOR₁₁,
- 20 (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄, (CR₁₀R₂₀)_nNO₂, (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nSO₂R₁₈, (CR₁₀R₂₀)_nS(O)_m"NR₁₃R₁₄, (CR₁₀R₂₀)_nC(Z)R₁₁, (CR₁₀R₂₀)_nOC(Z)R₁₁, (CR₁₀R₂₀)_nC(Z)OR₁₁, (CR₁₀R₂₀)_nC(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nC(Z)NR₁₁OR₉, (CR₁₀R₂₀)_nNR₁₀C(Z)R₁₁, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄,
- 25 (CR₁₀R₂₀)_nN(OR₆)C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nN(OR₆)C(Z)R₁₁, (CR₁₀R₂₀)_nC(=NOR₆)R₁₁, (CR₁₀R₂₀)_nNR₁₀C(=NR₁₉)NR₁₃R₁₄, (CR₁₀R₂₀)_nOC(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nNR₁₀C(Z)OR₁₀, 5-(R₁₈)-1,2,4-oxadiazol-3-yl or 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cycloalkyl, cycloalkyl alkyl, heterocyclic and
- 30 heterocyclic alkyl groups may be optionally substituted;

- n is an integer having a value of 1 to 10;
n' is 0, or an integer having a value of 1 to 10;
Z is oxygen or sulfur;
R₃ is heterocyclyl, heterocyclylC₁₋₁₀ alkyl or R₈;
- 5 R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being -SOH;
- R₆ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroaryl₁₋₄alkyl, heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;
- 10 R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;
- R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈,
15 (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
- R₉ is hydrogen, -C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;
- 20 R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;
- R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl;
- R₁₂ is hydrogen or R₁₆;
- R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted
25 C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉ ;
- R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;
- 30 R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;

R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, aryl-C₁₋₁₀alkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroaryl-C₁₋₁₀alkyl;

R₁₉ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

5

DETAILED DESCRIPTION OF THE INVENTION

In Formula (I), suitable R₁ moieties includes 4-pyridyl, 4-pyrimidinyl, 4-quinolyl, 6-isoquinolyl, 4-quinazolyl, 1-imidazolyl and 1-benzimidazolyl, of which the 4-pyridyl, 4-pyrimidinyl and 4-quinolyl are preferred. More preferred is the 4-pyrimidinyl or 4-pyridyl moiety, and most preferred is the 4-pyrimidinyl ring. The R₁ moiety is substituted with NHR_a, wherein R_a is aryl, aryl-C₁₋₆alkyl, heterocyclic, heterocyclic C₁₋₆ alkyl, heteroaryl, or heteroaryl C₁₋₆alkyl; and wherein each of these moieties may be optionally substituted.

When R_a is aryl, it is preferably phenyl or naphthyl. When R_a is aryl alkyl, it is preferably benzyl or naphthylmethyl. When R_a is heterocyclic or heterocyclic alkyl moiety the heterocycle is preferably pyrrolindinyl, piperidine, morpholino, tetrahydropyran, tetrahydrothiopyranyl, tetrahydrothiopyransulfinyl, tetrahydrothiopyransulfonyl, pyrrolindinyl, or piperonyl, more preferably piperidine.

When R_a is a heteroaryl or heteroaryl alkyl, it is heteroaryl is preferably imidazole, indole, pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, or benzimidazole, more preferably imidazole, or indole.

As noted above, the aryl, heterocyclic and heteroaryl rings may be optionally substituted, one or more times, preferably 1 to 3 times, independently, by halogen; C₁₋₄ alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted alkyl, such as CF₃; hydroxy; hydroxy substituted C₁₋₄ alkyl; C₁₋₄ alkoxy, such as methoxy or ethoxy; S(O)_malkyl and S(O)_m aryl (wherein m is 0, 1, or 2); C(O)OR₁₁, such as C(O)C₁₋₄ alkyl or C(O)OH moieties; C(O)R₁₁; OC(O)R₁₈, wherein the R₁₈ moiety may be optionally substituted as herein described below; O-(CH₂)_s-O-, such as in a ketal or dioxyalkylene bridge and s is an integer of 1 to 3; amino; mono- and di-C₁₋₆ alkylsubstituted amino; N(R₁₀)C(O)R_b; an N-heterocyclyl ring which ring has from 5

to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅; optionally substituted aryl, such as phenyl; or an optionally substituted aryl C₁₋₄ alkyl, such as benzyl or phenethyl.

Suitably, in compounds of Formula (I) R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl.

Suitable R_a groups include, benzyl, halosubstituted benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, morpholinopropyl, imidazole propyl, ethyl-1-piperidine-carboxylate, piperonyl, piperidin-4-yl, alkyl substituted piperidine, such as 1-methyl piperidine, or 2,2,6,6-tetramethylpiperidin-4-yl, chlorotryptamine, tetrahydrothiopyranyl, ethyl- N-C(O) O t-butyl, propylethoxy, 2-aminoethyl, propylimidazole.

It is recognized that the R₁ group may additionally be substituted by C₁₋₄ alkyl, halo, OH, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono- and di-C₁₋₆ alkylsubstituted amino, N(R₁₀)C(O)R_b, NHR_a or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅. Suitably, when the additional group is other than a dialkylsubstitued amino.

When the additional R₁ optional substituent is N(R₁₀)C(O) R_b, R_b is preferably C₁₋₆ alkyl; preferably R₁₀ is hydrogen. It is also recognized that the R_b moieties, in particular the C₁₋₆ alkyl group may be optionally substituted, preferably from one to three times, preferably with halogen, such as fluorine, as in trifluoromethyl or trifluoroethyl.

The preferred ring placement on the R₁ substituent for NHR_a, on the 4-pyridyl derivative is the 2-position, such as 2-(4-piperidinylamino)-4-pyridyl. A preferred ring placement on the 4-pyrimidinyl ring is also at the 2-position, such as in 2-benzyl-4-piperidinylamino pyrimidin-4-yl, 2-[3-(morpholino)propyl]amino pyrimidin-4-yl or 2-(3-bromophenyl)aminopyrimidin-4-yl.

Suitably, R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents. More preferably R₄ is a phenyl or naphthyl ring. Suitable substitutions for R₄ when this is a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl moiety are one or two substituents each of which are

independently selected from halogen, -SR₅, -SOR₅, -OR₁₂, CF₃, or (CR₁₀R₂₀)_vNR₁₀R₂₀, and for other positions of substitution on these rings preferred substitution is halogen, -S(O)_mR₃, -OR₃, CF₃, -(CR₁₀R₂₀)_mNR₁₃R₁₄, NR₁₀C(Z)R₃ and NR₁₀S(O)_mR₈. Preferred substituents for the 4-position in phenyl and naphth-1-yl and on the 5-position in naphth-2-yl include halogen, especially fluoro and chloro and -SR₅ and -SOR₅ wherein R₅ is preferably a C₁₋₂ alkyl, more preferably methyl; of which the fluoro and chloro is more preferred, and most especially preferred is fluoro. Preferred substituents for the 3-position in phenyl and naphth-1-yl rings include: halogen, especially fluoro and chloro; -OR₃, especially C₁₋₄ alkoxy; CF₃, NR₁₀R₂₀, such as amino; NR₁₀C(Z)R₃, especially -NHCO(C₁₋₁₀ alkyl); NR₁₀S(O)_mR₈, especially NHSO₂(C₁₋₁₀ alkyl), and -SR₃ and -SOR₃ wherein R₃ is preferably a C₁₋₂ alkyl, more preferably methyl. When the phenyl ring is disubstituted preferably it is two independent halogen moieties, such as fluoro and chloro, preferably di-chloro and more preferably in the 3,4-position. It is also preferred that for the 3-position of both the -OR₃ and -ZC(Z)R₃ moieties, R₃ may also include hydrogen.

Preferably, the R₄ moiety is an unsubstituted or substituted phenyl moiety. More preferably, R₄ is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C₁₋₄ alkoxy, methane-sulfonamido or acetamido, or R₄ is a phenyl di-substituted at the 3,4-position independently with chloro or fluoro, more preferably chloro. Most preferably, R₄ is a 4-fluorophenyl.

In Formula (I), Z is oxygen or sulfur, preferably oxygen.

Suitably, R₂ is -(CR₁₀R₂₀)_n OR₉, heterocyclyl, heterocyclylC₁₋₁₀ alkyl, C₁₋₁₀alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇ cycloalkenyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄, (CR₁₀R₂₀)_nNO₂, (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nSO₂R₁₈, (CR₁₀R₂₀)_nS(O)_mNR₁₃R₁₄, (CR₁₀R₂₀)_nC(Z)R₁₁, (CR₁₀R₂₀)_nOC(Z)R₁₁, (CR₁₀R₂₀)_nC(Z)OR₁₁, (CR₁₀R₂₀)_nC(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nC(Z)NR₁₁OR₉, (CR₁₀R₂₀)_nNR₁₀C(Z)R₁₁, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nN(OR₆)C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nN(OR₆)C(Z)R₁₁,

(CR₁₀R₂₀)_nC(=NOR₆)R₁₁, (CR₁₀R₂₀)_nNR₁₀C(=NR₁₉)NR₁₃R₁₄,
 (CR₁₀R₂₀)_nOC(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄,
 (CR₁₀R₂₀)_nNR₁₀C(Z)OR₁₀, 5-(R₁₈)-1,2,4-oxadiazol-3-yl or
 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the cycloalkyl,
 5 cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic, and
 heterocyclic alkyl moieties may be optionally substituted; wherein n is an integer having
 a value of 1 to 10, m is 0, or the integer 1 or 2; n' is 0, or an integer having a value of 1
 to 10; and m' is an integer having a value of 1 or 2. Preferably n is 1 to 4.

10 When R₂ is an optionally substituted heterocyclyl the ring is preferably a
 morpholino, pyrrolidinyl, or a piperidinyl group. When the ring is optionally substituted
 the substituents may be directly attached to the free nitrogen, such as in the piperidinyl
 group or pyrrole ring, or on the ring itself. Preferably the ring is a piperidine or pyrrole,
 more preferably piperidine. The heterocyclyl ring may be optionally substituted one to
 15 four times independently by halogen; C₁₋₄ alkyl; aryl, such as phenyl; aryl alkyl, such as
 benzyl - wherein the aryl or aryl alkyl moieties themselves may be optionally substituted
 (as in the definition section below); C(O)OR₁₁, such as the C(O)C₁₋₄ alkyl or C(O)OH
 moieties; C(O)H; C(O)C₁₋₄ alkyl, hydroxy substituted C₁₋₄ alkyl, C₁₋₄ alkoxy,
 S(O)_mC₁₋₄ alkyl (wherein m is 0, 1, or 2), NR₁₀R₂₀ (wherein R₁₀ and R₂₀ are
 20 independently hydrogen or C₁₋₄alkyl).

Preferably if the ring is a piperidine, the ring is attached to the imidazole at the 4-
 position, and the substituents are directly on the available nitrogen, i.e. a
 1-Formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxycarbonyl-
 4-piperidine. If the ring is substituted by an alkyl group and the ring is attached in the
 25 4-position, it is preferably substituted in the 2- or 6- position or both, such as 2,2,6,6-
 tetramethyl-4-piperidine. Similarly, if the ring is a pyrrole, the ring is attached to the
 imidazole at the 3-position, and the substituents are all directly on the available nitrogen.

When R₂ is an optionally substituted heterocyclyl C₁₋₁₀ alkyl group, the ring is
 preferably a morpholino, pyrrolidinyl, or a piperidinyl group. Preferably this alkyl
 30 moiety is from 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl
 group. Preferred heterocyclic alkyl groups include but are not limited to, morpholino

ethyl, morpholino propyl, pyrrolidinyl propyl, and piperidinyl propyl moieties. The heterocyclic ring herein is also optionally substituted in a similar manner to that indicated above for the direct attachment of the heterocyclyl.

- When R₂ is an optionally substituted C₃₋₇cycloalkyl, or an optionally substituted C₃₋₇cycloalkyl C₁₋₁₀ alkyl, the cycloalkyl group is preferably a C₄ or C₆ ring, most preferably a C₆ ring, which ring is optionally substituted. The cycloalkyl ring may be optionally substituted one to three times independently by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; C₁₋₁₀ alkoxy, such as methoxy or ethoxy; S(O)_m alkyl, wherein m is 0, 1, or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; S(O)_m aryl; cyano, nitro, amino, mono & di-substituted amino, such as in the NR₇R₁₇ group, wherein R₇ and R₁₇ are as defined in Formula (I); N(R₁₀)C(O)R₁₈; -preferably N(R₁₀)C(O)X₁ (wherein R₁₀ is as defined for Formula (I)), and X₁ is C₁₋₄ alkyl, aryl or arylC₁₋₄alkyl; N(R₁₀)C(O) aryl; C₁₋₁₀ alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; optionally substituted alkyl wherein the substituents are halogen, (such as CF₃), hydroxy, nitro, cyano, amino, mono & di-C₁₋₄ alkyl substituted amino; S(O)_m alkyl and S(O)_m aryl, wherein m is 0, 1 or 2; optionally substituted alkylene, such as ethylene or propylene; optionally substituted alkyne, such as ethyne; C(O)OR₁₁ (wherein R₁₁ is as defined in Formula (I)), such as the free acid or methyl ester derivative; the group R_C; -C(O)H; =O; =N-OR₁₁; -N(H)-OH (or substituted alkyl or aryl derivatives thereof on the nitrogen or on the oxime moiety); -N(OR_d)-C(O)-R₆; optionally substituted aryl, such as phenyl; optionally substituted arylC₁₋₄alkyl, such as benzyl or phenethyl; optionally substituted heterocycle or heterocyclic C₁₋₄alkyl, and further these aryl, arylalkyl, heterocyclic, and heterocyclic alkyl moieties may be optionally substituted one to two times, independently by halogen, hydroxy, C₁₋₁₀ alkoxy, S(O)_m alkyl, cyano, nitro, amino, mono & di-C₁₋₄ alkyl substituted amino, alkyl, or halosubstituted alkyl.

Suitably the group R_C is a 1,3-dioxyalkylene group of the formula -O-(CH₂)_s-O-, wherein s is 1 to 3, preferably s is 2 yielding a 1,3-dioxyethylene moiety, or ketal functionality.

- Suitably R_d is hydrogen, a pharmaceutically acceptable cation, aroyl or a C₁₋₁₀ alkanoyl group.

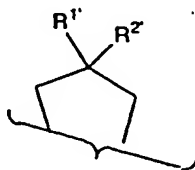
Suitably R_6' is $NR_{19}'R_{20}'$, C_{1-6} alkyl; halosubstituted C_{1-6} alkyl; hydroxy substituted C_{1-6} alkyl; alkenyl 2-6; aryl or heteroaryl optionally substituted by halogen, C_{1-6} alkyl, halosubstituted C_{1-6} alkyl, hydroxyl, or C_{1-6} alkoxy.

Suitably R_{19}' is H or alkyl₁₋₆.

- 5 Suitably R_{20}' is H, alkyl₁₋₆, aryl, benzyl, heteroaryl, alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, alkyl₁₋₁₂, alkoxy₁₋₆, halosubstituted alkyl₁₋₆, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R_{19}' and R_{20}' may together with the nitrogen to which they are attached form a ring having 5 to 7 members, which members may be optionally replaced by a
- 10 heteroatom selected from oxygen, sulfur or nitrogen. The ring may be saturated or contain more than one unsaturated bond. Preferably R_6' is $NR_{19}'R_{20}'$ and R_{19}' and R_{20}' are preferably hydrogen.

- When the R_2 cycloalkyl moiety is substituted by NR_7R_{17} group, or $NR_7R_{17}C_{1-10}$ alkyl group, and the R_7 and R_{17} are as defined in Formula (I), the
- 15 substituent is preferably an amino, amino alkyl, or an optionally substituted pyrrolidinyl moiety.

A preferred ring placement on the cycloalkyl moiety is the 4-position, such as in a C_6 ring. When the cycloalkyl ring is di-substituted it is preferably di-substituted at the 4 position, such as in:



- 20 wherein R_1' and R_2' are independently the optional substituents indicated above for R_2 as an optionally substituted cycloalkyl. Preferably, R_1' and R_2' are hydrogen, hydroxy, alkyl, substituted alkyl, optionally substituted alkyne, aryl, arylalkyl, NR_7R_{17} , and $N(R_{10})C(O)R_{18}$. Suitably, alkyl is C_{1-4} alkyl, such as methyl, ethyl, or isopropyl;
- 25 NR_7R_{17} and NR_7R_{17} alkyl, such as amino, methylamino, aminomethyl, aminoethyl; substituted alkyl such as in cyanomethyl, cyanoethyl, nitroethyl, pyrrolidinyl; aryl such as in phenyl; arylalkyl, such as in benzyl; optionally substituted alkyne, such as ethyne or propynyl; or together R_1' and R_2' are a keto functionality.

When R₂ is (CR₁₀R₂₀)_nNR₁₃R₁₄, wherein R₁₃ and R₁₄ are independently selected from hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl or an optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are
 5 attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉. It is recognized that in some instances this can yield the same moiety as a heterocyclic C₁₋₁₀ alkyl moiety noted above which is also a suitable R₂ variable. Preferably R₁₃ and R₁₄ are independently hydrogen, C₁₋₄ alkyl, preferably methyl, or benzyl. The n term is preferably 1 to 4,
 10 more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred groups include, but are not limited to, aminopropyl, (N-methyl-N-benzyl)aminopropyl, (N-Phenylmethyl)amino-1-propyl, or diethylamino propyl.

When R₂ is a (CR₁₀R₂₀)_nC(Z)OR₁₁ group, R₁₁ is suitably hydrogen, C₁₋₄ alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as
 15 in an ethyl or propyl group. Preferred groups include, but are not limited to, carboxymethyl-1-butyl, carboxy-1-propyl, or 2-acetoxyethyl.

When R₂ is a (CR₁₀R₂₀)_nS(O)_mR₁₈ group m is 0, 1, or 2, and R₁₈ is preferably aryl, especially phenyl, or C₁₋₁₀ alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

20 When R₂ is a (CR₁₀R₂₀)_nOR₁₁ group, R₁₁ is suitably hydrogen, aryl, especially phenyl, or C₁₋₁₀ alkyl, especially methyl or ethyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R₂ is a (CR₁₀R₂₀)_nNHS(O)₂R₁₈ group, R₁₈ is suitably alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or
 25 propyl group.

When R₂ is a optionally substituted aryl, the aryl is preferably phenyl. The aryl ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from C₁₋₄ alkyl, halogen, especially fluoro or chloro, (CR₁₀R₂₀)_iOR₁₁, -(CR₁₀R₂₀)_iNR₁₀R₂₀, especially amino or mono- or di-alkylamino -
 30 (CR₁₀R₂₀)_iS(O)_mR₁₈, wherein m is 0, 1 or 2; SH-, (CR₁₀R₂₀)_nNR₁₃R₁₄, NR₁₀C(Z)R₃ (such -NHCO(C₁₋₁₀ alkyl)); -NR₁₀S(O)_mR₈ (such as -NHSO₂(C₁₋₁₀

alkyl)); and t is 0, or an integer of 1 to 4. Preferably the phenyl is substituted in the 3 or 4- position by $-(\text{CR}_{10}\text{R}_{20})_t\text{S}(\text{O})_m\text{R}_{18}$, and R_{18} is preferably C_{1-10} alkyl, especially methyl.

When R_2 is an optionally substituted heteroaryl or heteroarylalkyl group the ring
 5 may be optionally substituted one or more times, preferably by one or two substituents, independently selected from one or more times, by C_{1-4} alkyl, halogen, especially fluoro or chloro, $(\text{CR}_{10}\text{R}_{20})_t\text{OR}_{11}$, $-(\text{CR}_{10}\text{R}_{20})_t\text{NR}_{10}\text{R}_{20}$, especially amino or mono- or di-alkylamino $-(\text{CR}_{10}\text{R}_{20})_t\text{S}(\text{O})_m\text{R}_{18}$, wherein m is 0, 1 or 2; $-\text{SH}-$, $-(\text{CR}_{10}\text{R}_{20})_n\text{NR}_{13}\text{R}_{14}$, $-\text{NR}_{10}\text{C}(\text{Z})\text{R}_3$ (such $-\text{NHCO}(\text{C}_{1-10}$ alkyl)); $-\text{NR}_{10}\text{S}(\text{O})_m\text{R}_8$ (such as -
 10 $\text{NHSO}_2(\text{C}_{1-10}$ alkyl)); t is 0, or an integer of 1 to 4.

One skilled in the art would readily recognize that when R_2 is a $(\text{CR}_{10}\text{R}_{20})_n\text{OC}(\text{Z})\text{R}_{11}$, or $(\text{CR}_{10}\text{R}_{20})_n\text{OC}(\text{Z})\text{NR}_{13}\text{R}_{14}$ moiety, or any similarly substituted group that n is preferably at least 2 which will allow for the synthesis of stable compounds.

15

Preferably R_2 is an optionally substituted heterocyclyl ring, and optionally substituted heterocyclyl C_{1-10} alkyl, an optionally substituted C_{1-10} alkyl, an optionally substituted C_{3-7} cycloalkyl, an optionally substituted C_{3-7} cycloalkyl C_{1-10} alkyl, $(\text{CR}_{10}\text{R}_{20})_nC(\text{Z})\text{OR}_{11}$ group, $(\text{CR}_{10}\text{R}_{20})_n\text{NR}_{13}\text{R}_{14}$, $(\text{CR}_{10}\text{R}_{20})_n\text{NHS}(\text{O})_2\text{R}_{18}$,
 20 $(\text{CR}_{10}\text{R}_{20})_n\text{S}(\text{O})_m\text{R}_{18}$, an optionally substituted aryl; an optionally substituted aryl C_{1-10} alkyl, $(\text{CR}_{10}\text{R}_{20})_n\text{OR}_{11}$, $(\text{CR}_{10}\text{R}_{20})_nC(\text{Z})\text{R}_{11}$, or $(\text{CR}_{10}\text{R}_{20})_nC(=\text{NOR}_6)\text{R}_{11}$ group.

More preferably R_2 is an optionally substituted heterocyclyl ring, and optionally substituted heterocyclyl C_{1-10} alkyl, optionally substituted aryl, optionally substituted
 25 C_{3-7} cycloalkyl, optionally substituted C_{3-7} cycloalkyl C_{1-10} alkyl, $(\text{CR}_{10}\text{R}_{20})_n\text{NR}_{13}\text{R}_{14}$, or $(\text{CR}_{10}\text{R}_{20})_nC(\text{Z})\text{OR}_{11}$ group.

Most preferably R_2 is an optionally substituted heterocyclic, heterocyclic C_{1-4} alkyl, a cycloalkyl or a cycloalkyl alkyl.

More preferably when R_2 is an optionally substituted cycloalkyl or
 30 cycloalkylalkyl it is a C_4 or C_6 cycloalkyl, cyclopropyl methyl, or a cyclohexyl substituted by methyl, phenyl, benzyl, amino, acetamide, aminomethyl, aminoethyl,

cyanomethyl, cyanoethyl, hydroxy, nitroethyl, pyrrolidinyl, ethynyl, 1-propynyl, =O, O-(CH₂)₂O-, =NOR₁₁, wherein R₁₁ is hydrogen, alkyl or aryl, NHOH, or N(OH)-C(O)-NH₂; or when R₂ is heterocyclic, or heterocyclialkyl, it is morpholinyl butyl, morpholinyl propyl, morpholinyl ethyl, piperidinyl, N-benzyl-4-piperidinyl, N-methyl-4-piperidinyl, 2,2,6,6-tetramethylpiperidinyl, substituted piperidine, such as 1-Formyl-4-piperidine, or a 1-ethoxycarbonyl-4-piperidine.

In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, the unsaturated linkage, i.e., the vinylene or acetylene linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties, for instance in OR₃, or for certain R₂ moieties.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy, such as methoxy or ethoxy; S(O)_m alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR₇R₁₇ group; or where the R₇R₁₇ may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C₁₋₁₀ alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C₁₋₁₀ alkyl, such CF₃; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C₁₋₁₀ alkoxy; S(O)_m alkyl; amino, mono & di-substituted amino, such as in the NR₇R₁₇ group; alkyl, or CF₃.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonc acid, ethane sulphonc acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable

cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- 5 • "halo" or "halogens", include the halogens: chloro, fluoro, bromo and iodo.
- "C₁₋₁₀alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- 10 • The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- The term "cycloalkenyl" is used herein to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.
- 15 • The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- 20 • "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- 25 • "heterocyclic" (on its own or in any combination, such as "heterocyclalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydro pyran, or imidazolidine.
- 30

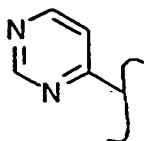
• The term "alkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C₁₋₄ alkyl as defined above attached to an aryl, heteroaryl or heterocyclic moiety as also defined herein unless otherwise indicate.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S (O)₂ moiety.

• "aroyl" - a C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivative such as defined above, such group include but are not limited to benzyl and phenethyl.

• "alkanoyl" - a C(O)C₁₋₁₀ alkyl wherein the alkyl is as defined above.

For the purposes herein the "core" 4-pyrimidinyl moiety for R₁ or R₂ is referred



to as the formula:

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

Exemplified compounds of Formula (I) include:

- 5-[(2-Benzylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-[2-(4-tetrahydrothiopyranyl)aminopyrimidin-4-yl]imidazole
- 4-(4-Fluorophenyl)-5-[(2-hydroxy)ethylamino]pyrimidin-4-yl-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(3-Chlorobenzylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(1-Naphthylmethylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(1-Benzyl-4-piperidinylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole

- 4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-[2-[3-(morpholino)propyl]-aminopyrimidin-4-yl]imidazole
- 5-[2[(3-Bromophenyl)amino]pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5 5-[(2(Piperonylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(4-Piperdinylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(5-Chlorotryptamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 10 5-[(2-(2,2,6,6-tetramethylpiperidin-4-yl)aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-[(1-Ethoxycarbonyl)piperdin-4-yl]aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 15 5-[2-(Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-oxocyclohexyl)imidazole
- 5-[4-(2-Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-hydroxycyclohexyl)-imidazole
- 4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-(2-phenylamino)pyrimidin-4-yl)-imidazole
- 20 4-(4-Fluorophenyl)-1-(2,2,6,6-tetramethylpiperdin-4-yl) 5-[(2-phenylamino)-pyrimidin-4-yl]imidazole
- 4-(4-Fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperdin-4-yl)imidazole
- 4-(4-Fluorophenyl)-5-[2-[3-[imidazol-1-yl]propyl]aminopyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperdin-4-yl]imidazole
- 25 4-(4-Fluorophenyl)-5-[2-[3-[imidazol-1-yl]propyl]aminopyrimidin-4-yl]-1-(piperdin-4-yl)imidazole
- 1-(4-Piperidiny)-4-(4-fluorophenyl)-5-(2-anilino-4-pyridinyl)imidazole

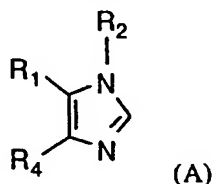
Another aspect of the present invention is the novel compounds of Formula (A), and pharmaceutical compositions comprising a compound of Formula (A) and a

30 pharmaceutically acceptable diluent or carrier.

This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in particular treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (A).

- 5 This invention more specifically relates to a method of inhibiting the production of IL-1, IL-6, IL-8 or TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (A).

Compounds of Formula (II) are represented by the structure:



- 10 R₁ is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is substituted with NHR_a and optionally with an additional independent substituent selected from C₁₋₄ alkyl, halogen, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, N(R₁₀)C(O)R_b or NHR_a;
- 15 R_a is C₁₋₆alkyl substituted one or more times, independently by halogen; hydroxy; C₁₋₁₀; S(O)_m alkyl, wherein m is 0, 1 or 2; amino, mono & di-C₁₋₄ alkyl substituted amino; C₃₋₇ cycloalkyl; C₃₋₇ cycloalkyloxy; or a moiety having the formula A₁- B₁- D₁:
- wherein A₁ is CR₁₀R₂₀, oxygen, sulfur, or NR₁₀R₂₀;
- 20 B₁ is C(O) or S(O)₂;
- D₁ is E₁ or E₂ wherein E₁ is C₁₋₁₀ alkyl, aryl, aryl C₁₋₆ alkyl, heteroaryl, heteroaryl C₂₋₆ alkenyl, heterocyclic, or heterocyclic C₁₋₆ alkyl; and E₂ is O-E₁ or N-E₁;
- R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl;
- 25 R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen,

cyano, nitro, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{16}$, $-(CR_{10}R_{20})_vCOR_{12}$, $-SR_5$, $-SOR_5$, $-OR_{12}$, halo-substituted- C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{12}$, $-NR_{10}C(Z)R_{16}$, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $-C(Z)NR_{13}R_{14}$, $-C(Z)OR_3$, $-(CR_{10}R_{20})_mCOR_3$, $-S(O)_mR_3$, $-OR_3$, halo-substituted- C_{1-4} alkyl, $-C_{1-4}$ alkyl, $-(CR_{10}R_{20})_mNR_{10}C(Z)R_3$, $-NR_{10}S(O)_mR_8$, $-NR_{10}S(O)_mNR_7R_{17}$, $-ZC(Z)R_3$ or $-(CR_{10}R_{20})_mNR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

10 m" is 0, or an integer having a value of 1 to 5;

R₂ is $-(CR_{10}R_{20})_nOR_9$, heterocyclyl, heterocyclyl C_{1-10} alkyl, C_{1-10} alkyl,

halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl,

C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, aryl,

aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$,

15 $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$,

$(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nSO_2R_{18}$,

$(CR_{10}R_{20})_nS(O)_mNR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$,

$(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$,

$(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$,

20 $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$,

$(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$,

$(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$,

$(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-(R₁₈)-1,2,4-oxadizaol-3-yl or

4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl,

25 heteroaryl, heteroaryl alkyl, cycloalkyl, cycloalkyl alkyl, heterocyclic and

heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

30 R₃ is heterocyclyl, heterocyclyl C_{1-10} alkyl or R₈;

- R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being -SOH;
- R₆ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroaryl₁₋₄alkyl, heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;
- 5 R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;
- 10 R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
- 15 R₉ is hydrogen, -C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;
- R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;
- R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl;
- R₁₂ is hydrogen or R₁₆;
- 20 R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉ ;
- 25 R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;
- R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;
- R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, aryl₁₋₁₀alkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroaryl₁₋₁₀alkyl;
- R₁₉ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;
- 30 or a pharmaceutically acceptable salt thereof.

For compounds of Formula (A), R_1 through R_{20} , R_b , v , m , m' , m'' , n , n' , Z , and all remaining variables but for the R_a term, are the same as those defined above for Formula (I).

Suitably, in compounds of Formula (A), R_a moiety is a substituted alkyl group, where the alkyl moiety is substituted one or more times, preferably 1 or 3 times, independently by halogen, such as fluorine, chlorine, bromine or iodine or multiple halogens, such as CF_3 ; hydroxy; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_m$ alkyl, wherein m is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di- C_{1-4} alkyl substituted amino; C_{3-7} cycloalkyl, or C_{3-7} cycloalkyloxy group, such as cyclopropyl or cyclopentyl, or a cyclohexyloxy; $A_1-B_1-D_1$ moiety wherein A_1 is $CR_{10}R_{20}$, oxygen, sulfur, or $NR_{10}R_{20}$ and $R_{10}R_{20}$ are as defined in Formula (I), which is independently hydrogen or C_{1-4} alkyl. Preferably, A_1 is $NR_{10}R_{20}$. B_1 is $C(O)$ or $S(O)_2$, preferably $C(O)$. D_1 is E_1 or E_2 wherein E_1 is C_{1-10} alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkenyl, heterocyclic, or heterocyclicalkyl; and E_2 is $O-E_1$ or $E-D_1$. Preferably D_1 is OE_1 , and preferably E_1 is a C_{1-10} alkyl group. Suitably, $A_1-B_1-D_1$ is $N-C(O)$ O - t -butyl.

Suitable R_a groups include, 2-hydroxyethyl, ethyl- $N-C(O)$ O t -butyl, propylethoxy, or 2-aminoethyl.

The preferred ring placement on the R_1 substituent for NHR_a , on the 4-pyridyl derivative is the 2-position, and a preferred ring placement on the 4-pyrimidinyl ring is also at the 2-position, similar to that of compounds of Formula (I).

Exemplified compounds of Formula (A) include;

- 4-(4-Fluorophenyl)-5-[(2-hydroxy)ethylamino]pyrimidin-4-yl-1-(1-methyl-piperdin-4-yl)imidazole
- 4-(4-Fluorophenyl)-5-[2-(2-hydroxy)ethylaminopyrimidin-4-yl]-1-(2,2,6,6-tetramethylpiperdin-4-yl)-imidazole
- 4-(4-Fluorophenyl)-5-[(2-(3-ethoxypropylamino))]pyrimidin-4-yl]-1-[(1- t -butoxycarbonyl)piperdin-4-yl]imidazole
- 4-(4-Fluorophenyl)-5-[(2-[t -butoxycarbonylamino]ethylamino]pyrimidin-4-yl]-1-[(1- t -butoxycarbonyl)piperdin-4-yl]imidazole

4-(4-Fluorophenyl)-5-[(2-aminoethyl)amino]pyrimidin-4-yl]-1-(piperdin-4-yl)-
imidazole

4-(4-Fluorophenyl)-5-[(2-ethoxypropyl)amino]pyrimidin-4-yl]-1-(piperdin-4-yl)-
imidazole

5

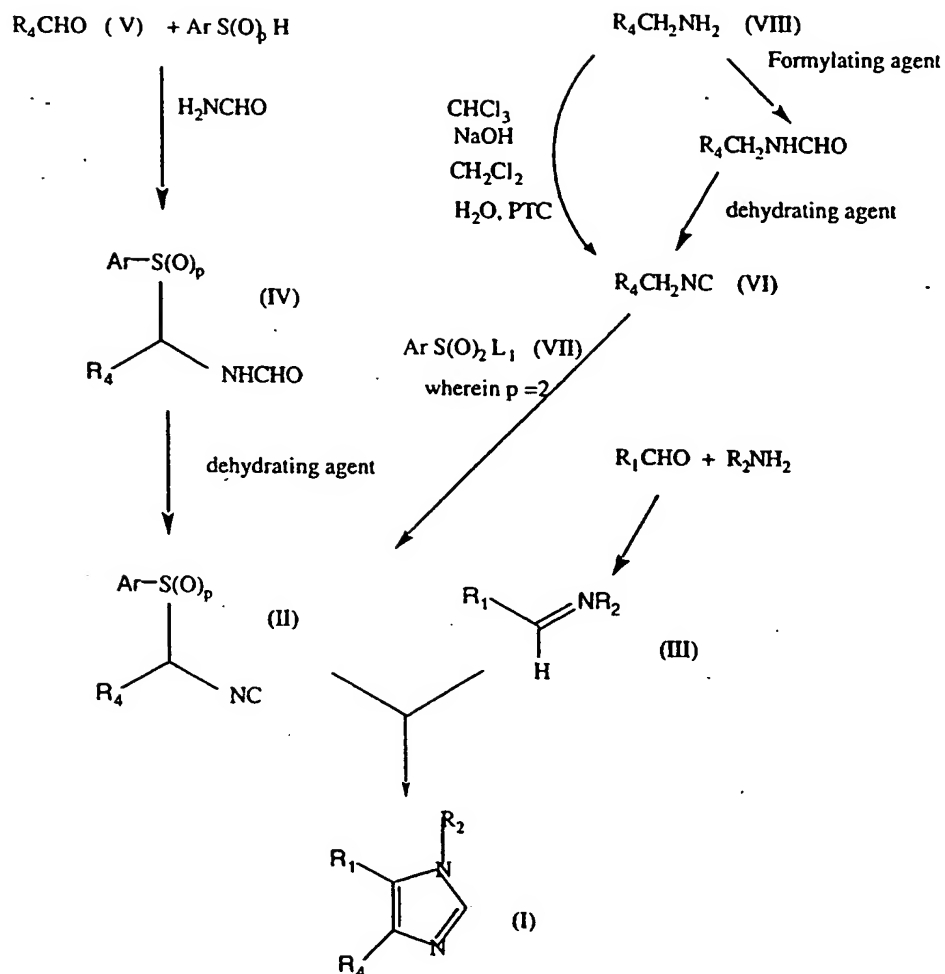
The compounds of Formula (I) and Formula (A) may be obtained by applying synthetic procedures, some of which are illustrated in Schemes I to XII herein. The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I) and Formula (A) having a variety of different R₁, R₂, and R₄ groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the imidazole nucleus has been established, further compounds of Formula (I) or Formula (A) may be prepared by applying standard techniques for functional group interconversion, well known in the art. In the synthetic procedures section discussed below, use of the term Formula (I) will also mean Formula (A) as they should be used interchangeably herein, except generally where indicated, as the noted procedures for making compounds of Formula (I) will also make compounds of Formula (A).

For instance: -C(O)NR₁₃R₁₄ from -CO₂CH₃ by heating with or without catalytic metal cyanide, e.g. NaCN, and HNR₁₃R₁₄ in CH₃OH; -OC(O)R₃ from -OH with e.g., ClC(O)R₃ in pyridine; -NR₁₀-C(S)NR₁₃R₁₄ from -NHR₁₀ with an alkylisothiocyanate or thiocyanic acid; NR₆C(O)OR₆ from -NHR₆ with the alkyl chloroformate; -NR₁₀C(O)NR₁₃R₁₄ from -NHR₁₀ by treatment with an isocyanate, e.g. HN=C=O or R₁₀N=C=O; -NR₁₀-C(O)R₈ from -NHR₁₀ by treatment with Cl-C(O)R₃ in pyridine; -C(=NR₁₀)NR₁₃R₁₄ from -C(NR₁₃R₁₄)SR₃ with H₃NR₃⁺OAc⁻ by heating in alcohol; -C(NR₁₃R₁₄)SR₃ from -C(S)NR₁₃R₁₄ with R₆-I in an inert solvent, e.g. acetone; -C(S)NR₁₃R₁₄ (where R₁₃ or R₁₄ is not hydrogen) from -C(S)NH₂ with HNR₁₃R₁₄-C(=NCN)-NR₁₃R₁₄ from -C(=NR₁₃R₁₄)-SR₃ with NH₂CN by heating in anhydrous alcohol, alternatively from -C(=NH)-NR₁₃R₁₄ by treatment with BrCN and NaOEt in EtOH; -NR₁₀-C(=NCN)SR₈ from -NHR₁₀ by treatment with (R₈S)₂C=NCN; -NR₁₀SO₂R₃ from -NHR₁₀ by treatment with ClSO₂R₃

by heating in pyridine; $-\text{NR}_{10}\text{C}(\text{S})\text{R}_3$ from $-\text{NR}_{10}\text{C}(\text{O})\text{R}_8$ by treatment with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; $-\text{NR}_{10}\text{SO}_2\text{CF}_3$ from $-\text{NHR}_6$ with triflic anhydride and base wherein R_3 , R_6 , R_{10} , R_{13} and R_{14} are as defined in Formula (I) herein.

- 5 Precursors of the groups R_1 , R_2 and R_4 can be other R_1 , R_2 and R_4 groups which can be interconverted by applying standard techniques for functional group interconversion. For example a compound of the formula (I) wherein R_2 is halo-substituted C_{1-10} alkyl can be converted to the corresponding C_{1-10} alkyl N_3 derivative by reacting with a suitable azide salt, and thereafter if desired can be reduced to the
- 10 corresponding C_{1-10} alkyl NH_2 compound, which in turn can be reacted with $\text{R}_{18}\text{S}(\text{O})_2\text{X}$ wherein X is halo (e.g., chloro) to yield the corresponding C_{1-10} alkyl $\text{NHS}(\text{O})_2\text{R}_{18}$ compound.

- Alternatively a compound of the formula (I) where R_2 is halo-substituted C_{1-10} -alkyl can be reacted with an amine $\text{R}_{13}\text{R}_{14}\text{NH}$ to yield the corresponding
- 15 C_{1-10} -alkyl $\text{NR}_{13}\text{R}_{14}$ compound, or can be reacted with an alkali metal salt of R_{18}SH to yield the corresponding C_{1-10} alkyl SR_{18} compound.



SCHEME I

Referring to Scheme I the compounds of Formula (I) are suitably prepared by

5 reacting a compound of the Formula (II) with a compound of the Formula (III) wherein p is 0 or 2, R_1 , R_2 and R_4 are as defined herein, for Formula (I), or are precursors of the groups R_1 , R_2 and R_4 , and Ar is an optionally substituted phenyl group, and thereafter if necessary converting a precursor of R_1 , R_2 and R_4 to a group R_1 , R_2 and R_4 .

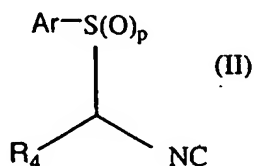
Suitably, the reaction is performed at ambient temperature or with cooling (e.g. -

10 50° to 10°) or heating in an inert solvent such as methylene chloride, DMF, tetrahydrofuran, toluene, acetonitrile, or dimethoxyethane in the presence of an appropriate base such as 1,8-diazabicyclo [5.4.0.] undec-7-ene (DBU) or a guanidine

base such as 1,5,7-triaza-bicyclo [4.4.0] dec-5-ene (TBD). The intermediates of formula (II) have been found to be very stable and capable of storage for a long time. Preferably, p is 2.

Compounds of the Formula (II) have the structure:

5



wherein p is 0, or 2; R₄ is as defined for Formula (I) and Ar is an optionally substituted aryl as defined herein. Suitably, Ar is phenyl optionally substituted by C₁₋₄alkyl, C₁₋₄ alkoxy or halo. Preferably Ar is phenyl or 4-methylphenyl, i.e. a tosyl derivative.

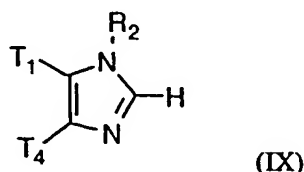
10 Reaction a compound of the Formula (II) wherein p = 2, with a compound of the Formula (III)-Scheme I gives consistently higher yields of compounds of Formula (I) than when p=0. In addition, the reaction of Formula (II) compounds wherein p = 2 is more environmentally and economically attractive. When p=0, the preferred solvent used is methylene chloride, which is environmentally unattractive for large scale
15 processing, and the preferred base, TBD, is also expensive, and produces some byproducts and impurities, than when using the commercially attractive synthesis (p=2) as further described herein.

As noted, Scheme I utilizes the 1,3-dipolar cycloadditions of an anion of a substituted aryl thiomethylisocyanide (when p=0) to an imine. More specifically, this
20 reaction requires a strong base, such as an amine base, to be used for the deprotonation step. The commercially available TBD is preferred although t-butoxide, Li⁺ or Na⁺, or K⁺ hexamethyldisilazide may also be used. While methylene chloride is the preferred solvent, other halogenated solvents, such as chloroform or carbon tetrachloride; ethers, such as THF, DME, DMF, diethylether, t-butyl methyl ether; as well as acetonitrile,
25 toluene or mixtures thereof can be utilized. The reaction may take place from about -20° C to about; 40° C, preferably from about 0° C to about 23° C, more preferably from about 0° C to about 10° C, and most preferably about 4° C for reactions involving an R₁ group of pyrimidine. For compounds wherein R₁ is pyridine, it is recognized that

varying the reactions conditions of both temperature and solvent may be necessary, such as decreasing temperatures to about -50°C or changing the solvent to THF.

In a further process, compounds of Formula (I) may be prepared by coupling a suitable derivative of a compound of Formula (IX):

5



wherein T₁ is hydrogen and T₄ is R₄, or alternatively T₁ is R₁ and T₄ is H in which R₁, R₂ and R₄ are as hereinbefore defined; with: (i) when T₁ is hydrogen, a suitable derivative of the heteroaryl ring R₁H, under ring coupling conditions, to effect coupling of the heteroaryl ring R₁ to the imidazole nucleus at position 5; (ii) when T₄ is hydrogen, a suitable derivative of the aryl ring R₄H, under ring coupling conditions, to effect coupling of the aryl ring R₄ to the imidazole nucleus at position 4.

Such aryl/heteroaryl coupling reactions are well known to those skilled in the art. In general, an organometallic synthetic equivalent of an anion of one component is coupled with a reactive derivative of the second component, in the presence of a suitable catalyst. The anion equivalent may be formed from either the imidazole of Formula (IX), in which case the aryl/heteroaryl compound provides the reactive derivative, or the aryl/heteroaryl compound in which case the imidazole provides the reactive derivative. Accordingly, suitable derivatives of the compound of Formula (IX) or the aryl/heteroaryl rings include organometallic derivatives such as organomagnesium, organozinc, organostannane and boronic acid derivatives and suitable reactive derivatives include the bromo, iodo, fluorosulfonate and trifluoromethanesulphonate derivatives. Suitable procedures are described in WO 91/19497, the disclosure of which is incorporated by reference herein.

Suitable organomagnesium and organozinc derivatives of a compound of Formula (IX) may be reacted with a halogen, fluorosulfonate or triflate derivative of the heteroaryl or aryl ring, in the presence of a ring coupling catalyst, such as a palladium

(O) or palladium (II) catalyst, following the procedure of Kumada *et al.*, Tetrahedron Letters, 22, 5319 (1981). Suitable such catalysts include *tetrakis*-(triphenylphosphine)palladium and $\text{PdCl}_2[1,4\text{-bis}-(\text{diphenylphosphino})\text{-butane}]$, optionally in the presence of lithium chloride and a base, such as triethylamine. In addition, a nickel (II) catalyst, such as $\text{Ni(II)Cl}_2(1,2\text{-biphenylphosphino})\text{ethane}$, may also be used for coupling an aryl ring, following the procedure of Pridgen *et al.*, J. Org. Chem, 1982, 47, 4319. Suitable reaction solvents include hexamethylphosphoramide. When the heteroaryl ring is 4-pyridyl, suitable derivatives include 4-bromo- and 4-iodo-pyridine and the fluorosulfonate and triflate esters of 4-hydroxy pyridine. Similarly, suitable derivatives for when the aryl ring is phenyl include the bromo, fluorosulfonate, triflate and, preferably, the iodo-derivatives. Suitable organomagnesium and organozinc derivatives may be obtained by treating a compound of Formula (IX) or the bromo derivative thereof with an alkyllithium compound to yield the corresponding lithium reagent by deprotonation or transmetalation, respectively. This lithium intermediate may then be treated with an excess of a magnesium halide or zinc halide to yield the corresponding organometallic reagent.

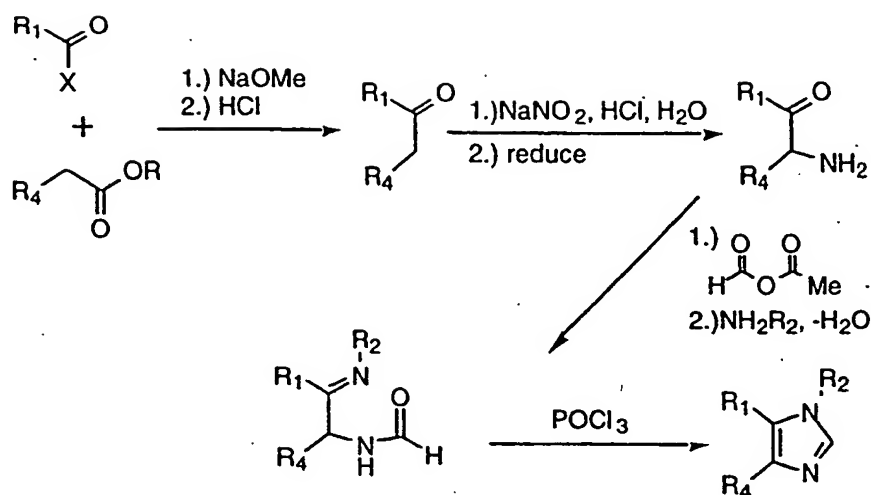
A trialkyltin derivative of the compound of Formula (IX) may be treated with a bromide, fluorosulfonate, triflate, or, preferably, iodide derivative of an aryl or heteroaryl ring compound, in an inert solvent such as tetrahydrofuran, preferably containing 10% hexamethylphosphoramide, in the presence of a suitable coupling catalyst, such as a palladium (0) catalyst, for instance *tetrakis*-(triphenylphosphine)-palladium, by the method described in by Stille, J. Amer. Chem. Soc, 1987, 109, 5478, US Patents 4,719,218 and 5,002,942, or by using a palladium (II) catalyst in the presence of lithium chloride optionally with an added base such as triethylamine, in an inert solvent such as dimethyl formamide. Trialkyltin derivatives may be conveniently obtained by metallation of the corresponding compound of Formula (IX) with a lithiating agent, such as *s*-butyl-lithium or *n*-butyllithium, in an ethereal solvent, such as tetrahydrofuran, or treatment of the bromo derivative of the corresponding compound of Formula (IX) with an alkyl lithium, followed, in each case, by treatment with a trialkyltin halide. Alternatively, the bromo- derivative of a compound of Formula (IX) may be treated with a suitable heteroaryl or aryl trialkyl tin compound in the presence of

a catalyst such as *tetrakis*-(triphenyl-phosphine)-palladium, under conditions similar to those described above.

Boronic acid derivatives are also useful. Hence, a suitable derivative of a compound of Formula (IX), such as the bromo, iodo, triflate or fluorosulphonate derivative, may be reacted with a heteroaryl- or aryl-boronic acid, in the presence of a palladium catalyst such as *tetrakis*-(triphenylphosphine)-palladium or $\text{PdCl}_2[1,4\text{-bis}(\text{diphenyl-phosphino})\text{-butane}]$ in the presence of a base such as sodium bicarbonate, under reflux conditions, in a solvent such as dimethoxyethane (see Fischer and Haviniga, Rec. Trav. Chim. Pays Bas, 84, 439, 1965, Snieckus, V., Tetrahedron Lett., 29, 2135, 1988 and Terashimia, M., Chem. Pharm. Bull., 11, 4755, 1985). Non-aqueous conditions, for instance, a solvent such as DMF, at a temperature of about 100°C, in the presence of a Pd(II) catalyst may also be employed (see Thompson W J *et al.*, J Org Chem, 49, 5237, 1984). Suitable boronic acid derivatives may be prepared by treating the magnesium or lithium derivative with a trialkylborate ester, such as triethyl, tri-*iso*-propyl or tributylborate, according to standard procedures.

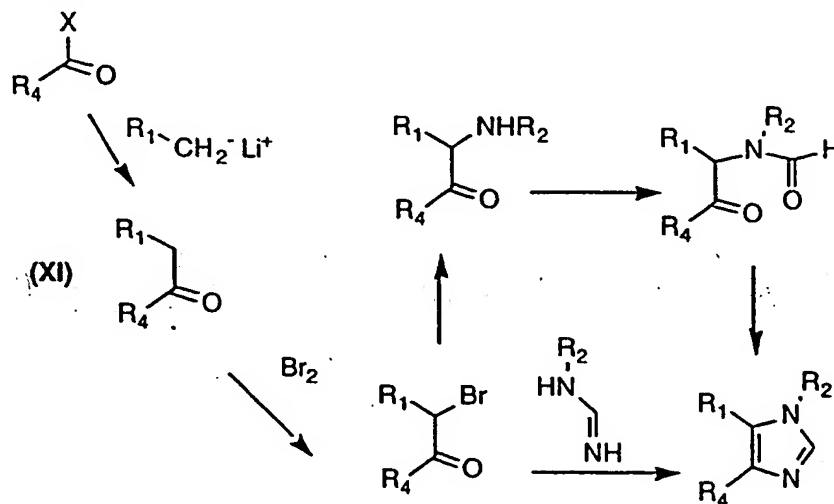
In such coupling reactions, it will be readily appreciated that due regard must be exercised with respect to functional groups present in the compounds of Formula (IX). Thus, in general, amino and sulfur substituents should be non-oxidised or protected.

As illustrated in Scheme II below, compounds of Formula (I) may be prepared by treating a compound of Formula (X) thermally or with the aid of a cyclising agent such as phosphorus oxychloride or phosphorus pentachloride (see Engel and Steglich, Liebigs Ann Chem, 1978, 1916 and Strzybny *et al.*, J Org Chem, 1963, 28, 3381). Compounds of Formula (X) may be obtained, for instance, by acylating the corresponding α -keto-amine with an activated formate derivative such as the corresponding anhydride, under standard acylating conditions followed by formation of the imine with R_2NH_2 . The aminoketone may be derived from the parent ketone by oxamination and reduction and the requisite ketone may in turn be prepared by decarboxylation of the beta-ketoester obtained from the condensation of an aryl (heteroaryl) acetic ester with the R_1COX component.



SCHEME II

In Scheme III illustrated below, two (2) different routes which use ketone (formula XI) for preparing a compound of Formula (I). A heterocyclic ketone (XI) is prepared by adding the anion of the alkyl heterocycle such as 4-methyl-quinoline (prepared by treatment thereof with an alkyl lithium, such as *n*-butyl lithium) to an N-alkyl-O-alkoxybenzamide, ester, or any other suitably activated derivative of the same oxidation state. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidised to the ketone (XI).



SCHEME III

In a further process, N-substituted compounds of Formula (I) may be prepared by treating the anion of an amide of Formula (XII):



wherein R₁ and R₂ with:

- 5 (a) a nitrile of the Formula (XIII):

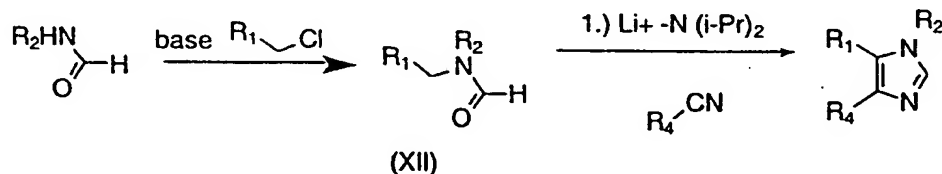


wherein R₄ is as hereinbefore defined, or

- (b) an excess of an acyl halide, for instance an acyl chloride, of the Formula (XIV):



- 10 wherein R₄ is as hereinbefore defined and Hal is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia, such as ammonium acetate.



15

SCHEME IV

One variation of this approach is illustrated in Scheme IV above. A primary amine (R₂NH₂) is treated with a halomethyl heterocycle of Formula R₁CH₂X to give the secondary amine which is then converted to the amide by standard techniques.

- 20 Alternatively the amide may be prepared as illustrated in scheme V by alkylation of the formamide with R₁CH₂X. Deprotonation of this amide with a strong amide base, such as lithium di-*iso*-propyl amide or sodium *bis*-(trimethylsilyl)amide, followed by addition of an excess of an aroyl chloride yields the *bis*-acylated compound which is then closed to an imidazole compound of Formula (I), by heating in acetic acid containing
- 25 ammonium acetate. Alternatively, the anion of the amide may be reacted with a substituted aryl nitrile to produce the imidazole of Formula (I) directly.

The following description and schemes are further exemplification of the process as previously described above in Scheme I. The reaction of imines with tosylmethyl isonitriles was first reported by van Leusen (van Leusen, et al., *J. Org. Chem.* 1977, 42, 1153.) Reported were the following conditions: tert butyl amine (*t*BuNH₂) in dimethoxyethane (DME), K₂CO₃ in MeOH, and NaH in DME. Upon re-examination of these conditions each was found produce low yields. A second pathway involving amine exchange to produce the *t*-butyl imine followed by reaction with the isocyanide to produce a 1-*t*Bu imidazole was also operating. This will likely occur using any primary amine as a base. The secondary amines, while not preferred may be used, but may also decompose the isonitrile slowly. Reactions will likely require about 3 equivalents of amine to go to completion, resulting in approximately 50% isolated yields. Hindered secondary amines (diisopropylamine) while usable are very slow and generally not too effective. Use of tertiary and aromatic amines, such as pyridine, and triethylamine gave no reaction under certain test conditions, but more basic types such as DBU, and 4-dimethylamino pyridine (DMAP) while slow, did produce some yields and hence may be suitable for use herein.

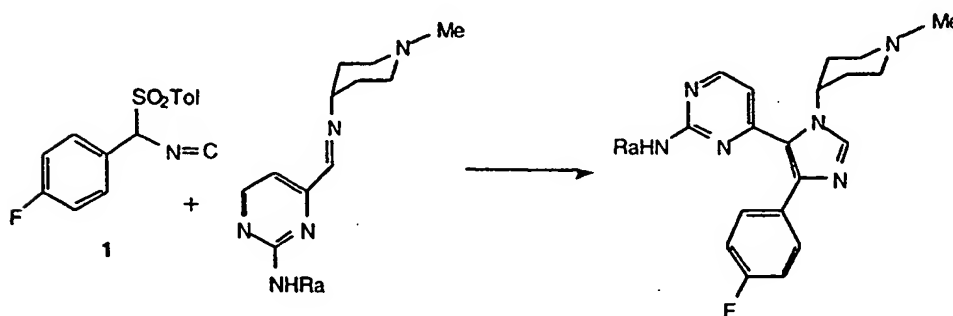
As depicted in Schemes V and VI below, the pyrimidine aldehydes of Scheme VII, can be condensed with a primary amine, to generate an imine, which may suitably be isolated or reacted in situ, with the desired isonitrile in the presence of a variety of suitable bases, and solvents as described herein to afford the 5-(4-pyrimidinyl)-substituted imidazoles, wherein R₂ and R₄ are as defined herein for Formula (I) compounds.

One preferred method for preparing compounds of Formula (I) is shown below in Scheme VI. The imines, prepared and isolated in a separate step were often tars, which were hard to handle. The black color was also often carried over into the final product. The yield for making the imines varied, and environmentally less-acceptable solvents, such as CH₂Cl₂ were often used in their preparation.

This reaction, wherein $p=2$, requires a suitable base for the reaction to proceed. The reaction requires a base strong enough to deprotonate the isonitrile. Suitable bases include an amine, a carbonate, a hydride, or an alkyl or aryl lithium reagent; or mixtures thereof. Bases include, but are not limited to, potassium carbonate, sodium carbonate,

primary and secondary amines, such as morpholine, piperidine, pyrrolidine, and other non-nucleophilic bases.

Suitable solvents for use herein, include but are not limited to *N,N*-dimethylformamide (DMF), MeCN, halogenated solvents, such as methylene chloride or chloroform, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, such as methanol or ethanol, benzene, or toluene, or DME. Preferably the solvent is DMF, DME, THF, or MeCN, more preferably DMF. Product isolation may generally be accomplished by adding water and filtering the product as a clean compound.



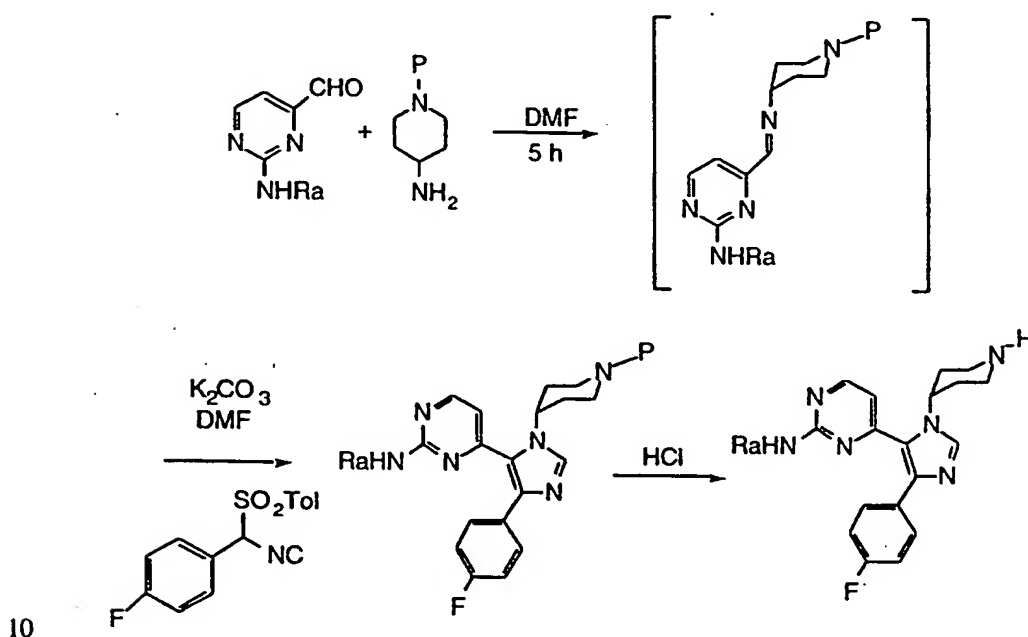
SCHEME V

While not convenient for large scale work, addition of NaH to the isonitrile, perhaps with temperatures lower than 25 °C (in THF) are likely needed. Additionally, BuLi has also been reported to be an effective base for deprotonating tosyl benzylisonitriles at -50 °C. (DiSanto, R.; Costi, R.; Massa, S.; Artico, M. *Synth. Commun.* 1995, 25, 795).

Various temperature conditions may be utilized depending upon the preferred base. For instance, $\text{tBuNH}_2/\text{DME}$, $\text{K}_2\text{CO}_3/\text{MeOH}$, K_2CO_3 in DMF, at temperatures above 40 °C, the yields may drop to about 20% but little difference is expected between 0 °C and 25 °C. Consequently, temperature ranges below 0 °C, and above 80 °C are contemplated as also being within the scope of this invention. Preferably, the temperature ranges are from about 0 °C to about 25 °C.

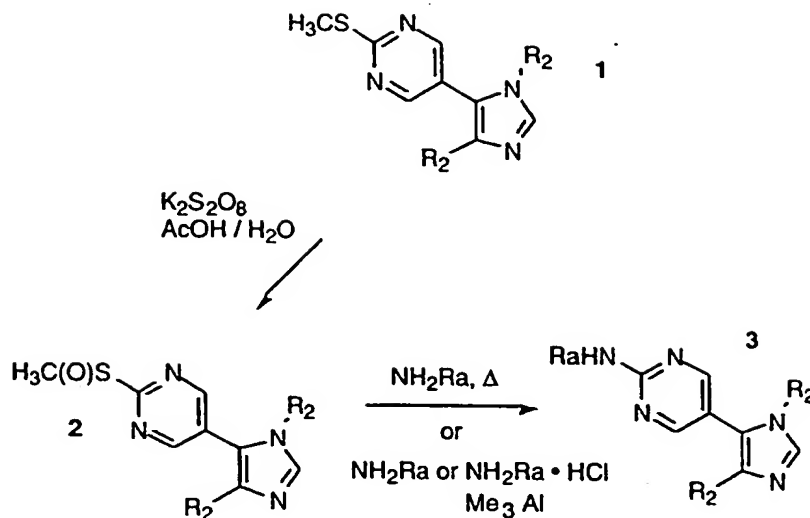
As shown in Scheme VI below, the imine is preferably formed in situ in a solvent. This preferred synthesis, is a process which occurs as a one-pot synthesis.

Suitably, when the primary amine is utilized as a salt, such as in the dihydrochloride salt in the Examples, the reaction may further include a base, such as potassium carbonate prior to the addition of the isonitrile. Alternatively, the piperidine nitrogen may be required to be protected for instance a t-butyl or ethyl carbamate or some other standard nitrogen protecting group. Reaction conditions, such as solvents, bases, temperatures, etc. are similar to those illustrated and discussed above for the isolated imine as shown in Scheme V. One skilled in the art would readily recognize that under some circumstances, the in situ formation of the imine may require dehydrating conditions, or may require acid catalysis.



SCHEME VI

Scheme VII describes an alternative process for making 2-aminopyrimidine containing compounds of formula (I). In this particular instance, the methylthio moiety is oxidized to the methylsulfinyl moiety which is reacted with a suitable NH_2Ra moiety. In cases in which NH_2Ra is an aliphatic amine (such as in compounds of Formula (A)), the methylsulfinyl moiety may be displaced directly with NH_2Ra at elevated temperatures. When Ra is an aromatic ring, (such as in compounds of Formula (I)), catalysis with trimethylaluminum may be required for displacement to occur.



Scheme VII

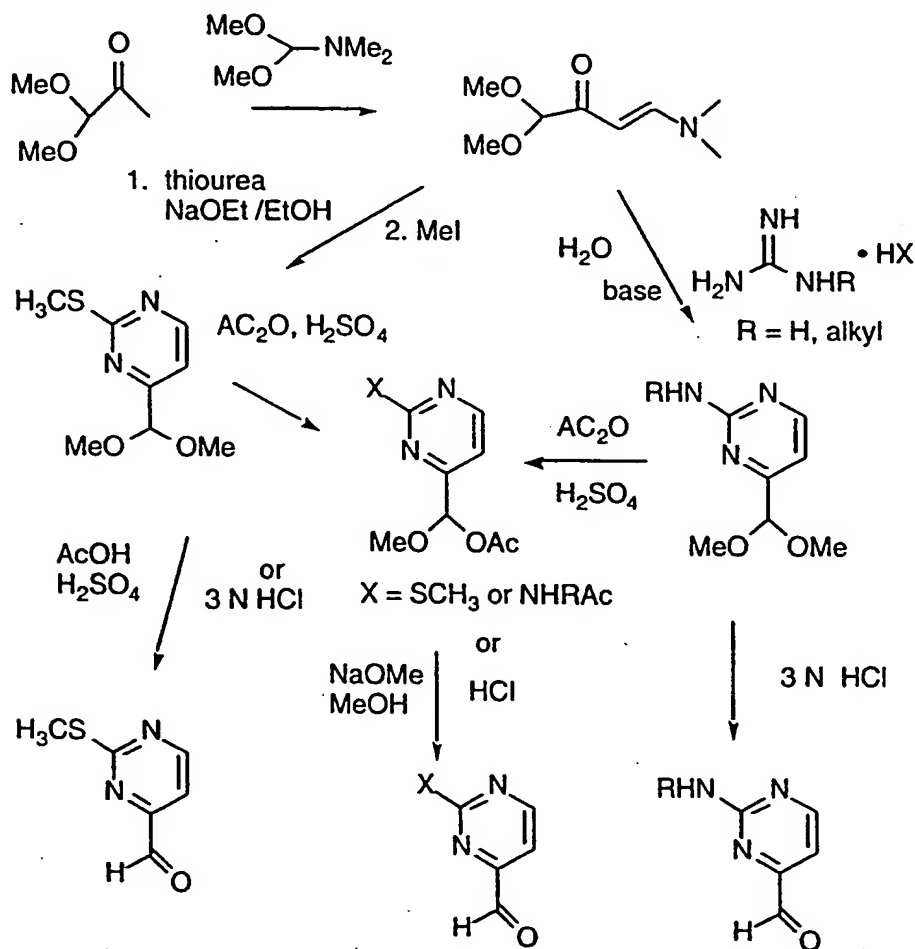
5 The dialkoxo acetals of 2-methylthiopyrimidine 4-carboxaldehyde and various 2-aminopyrimidine 4-carboxaldehydes can be prepared by modification of the procedures of Bredereck et al. (*Chem. Ber.* 1964, 97, 3407) whose disclosure is incorporated by reference herein and depicted below in scheme VIII. Hydrolysis of the acetals to

10 aldehyde using various known reaction conditions, such as formic acid, did not produce a satisfactory yields of the aldehydes. Development of novel hydrolysis procedures were, therefore, required and constitute another embodiment for the present invention. These hydrolysis procedures are illustrated in scheme VIII and are detailed in example 1. The preferred method of hydrolysis of the above mentioned acetals involves heating at 40-50

15 °C in 3 N HCl for 18 to 24 h followed by neutralization with solid NaHCO_3 and extraction with ethyl acetate. Evaporation of the solvent generally affords aldehyde suitable for direct imine formation. Column chromatography on silical gel increases overall yields in some cases. Hydrolysis of 2-methylthiopyrimidine 4-carboxaldehyde dimethyl acetal using acetic acid (fresh) as solvent and concentrated H_2SO_4 under heating conditions, preferably a catalytic amount of sulfuric acid, also affords the desired

20 aldehyde in high yield. Alternatively, 2-methylthiopyrimidine 4-carboxaldehyde dimethyl acetal and the various 2-aminopyrimidine 4-carboxaldehyde dimethyl acetals

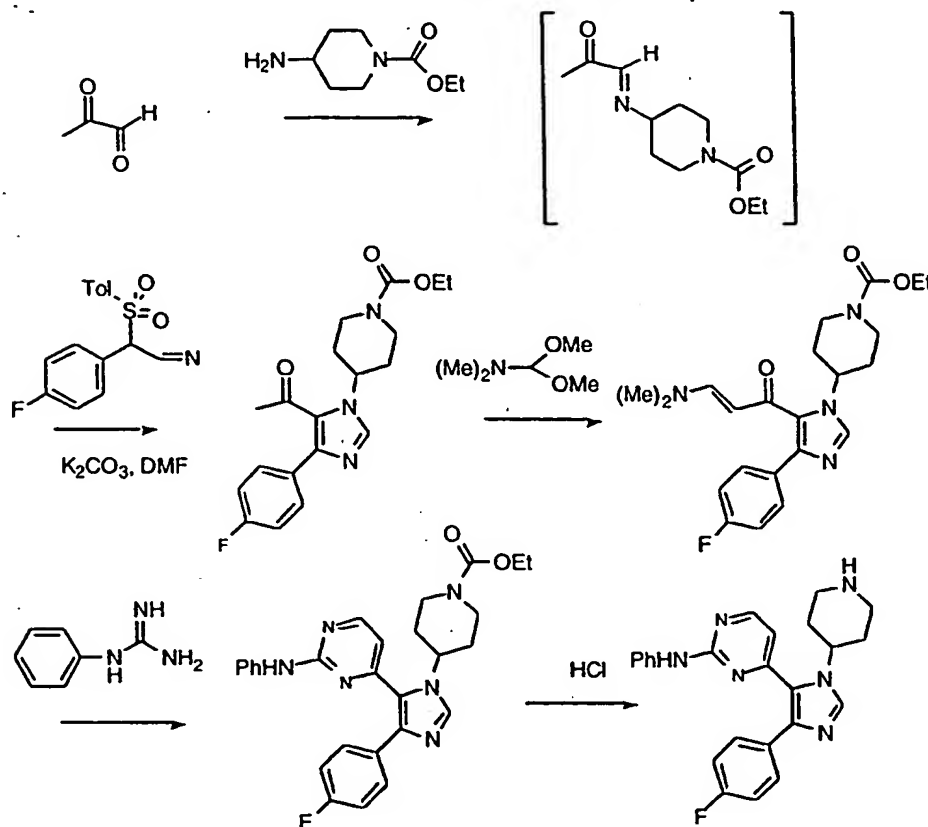
can be hydrolysed utilizing a two step acetolysis procedure. Treatment of the dialkoxy acetals with acetic anhydride containing a catalytic amount of sulfuric acid affords the mixed acyloxy-alkoxy acetals which can be converted to the corresponding aldehydes by treatment with either catalytic sodium methoxide in methanol or mild acid.



Scheme VIII

Pyrimidine containing compounds of Formula (I) can alternatively be prepared by assembling the pyrimidine ring on an already intact imidazole framework. A specific example of this synthetic approach is illustrated in scheme IX. While the scheme depicts and example in which R₂ is 4-piperidine and R₄ is 4-fluorophenyl, the method is generally applicable to any R₂ and R₄ substituents claimed in Formula (I). Likewise, the

method can be adapted to any substituted guanidine and, therefore, can be used to prepare any substituted pyrimidine moieties claimed for R₁ in Formula (I).



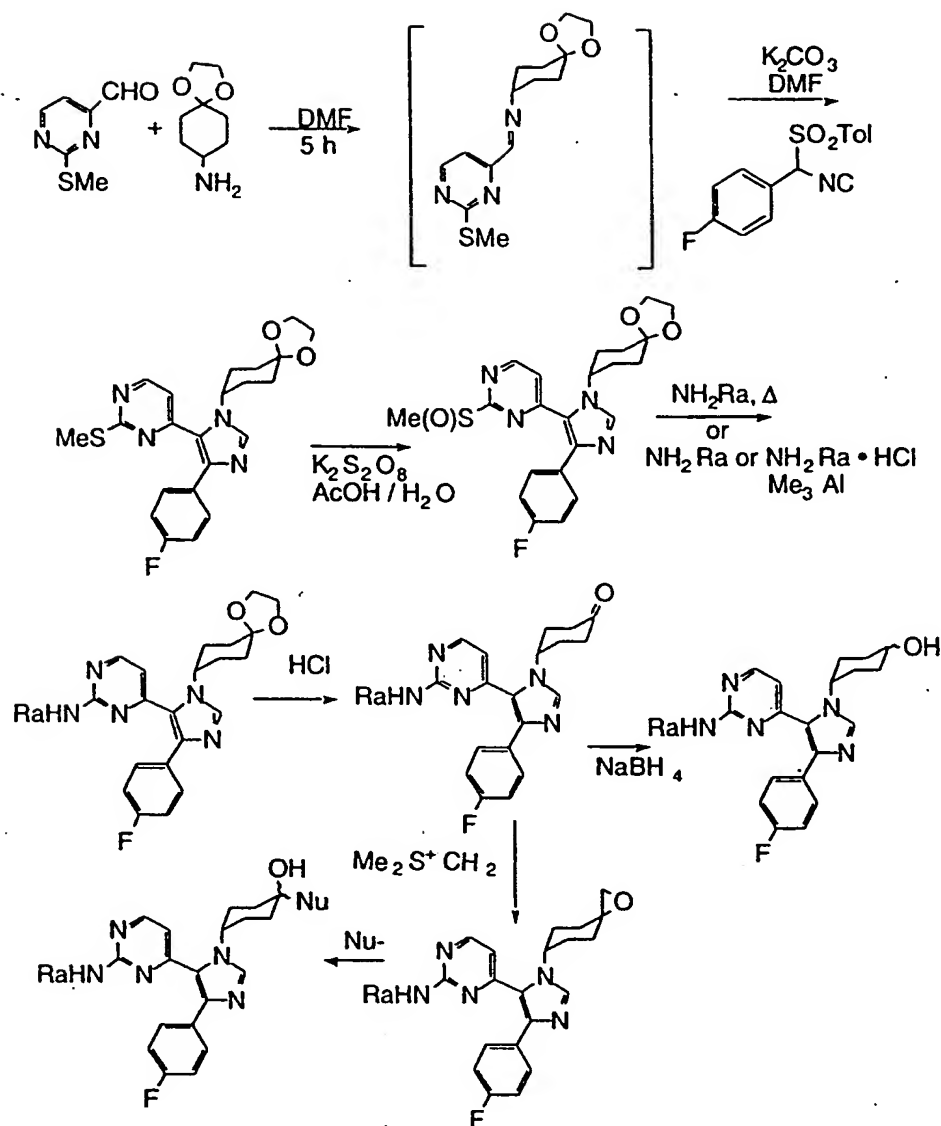
Scheme IX

5

- The final 2-alkyl or arylaminopyrimidin-4-yl imidazole compounds of Formula (I), compounds can be prepared by one of four methods: 1) direct reaction of the 2-aminopyrimidine imine with the isonitrile; 2) condensation of the 2-acetamidopyrimidine imine with the isonitrile followed by removal of the acetamido group; 3) oxidation of the 2-methylthiopyrimidine derivative to the corresponding sulfoxide followed by displacement with the desired amine and 4) assembling the desired alkyl or arylpyrimidine moiety on an intact imidazole by reacting the corresponding substituted guanidine with the desired 5-substituted N,N-dimethylamino-*trans*-1-propenone imidazole.
- 10

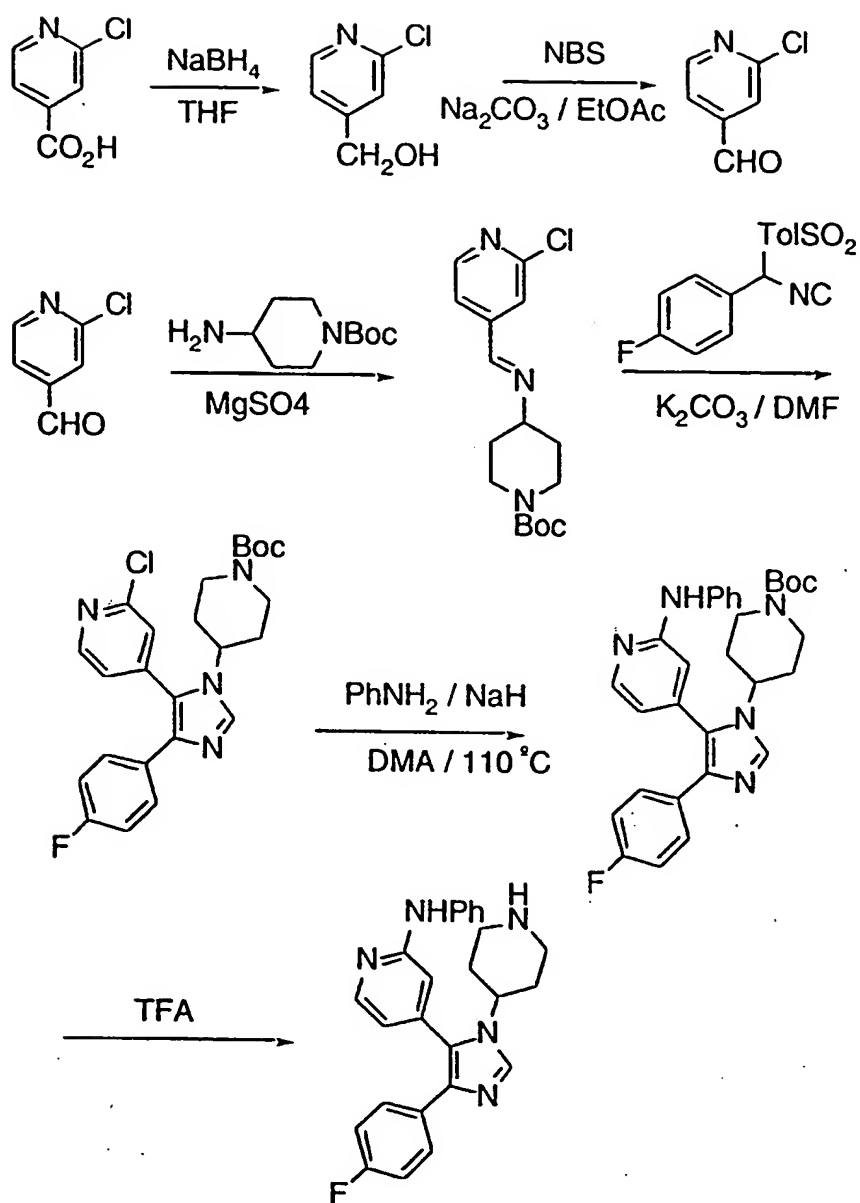
While these schemes herein are presented, for instance, with an optionally substituted piperidine moiety for the resultant R₂ position, or a 4-fluoro phenyl for R₄, any suitable R₂ moiety or R₄ moiety may be added in this manner if it can be prepared on the primary amine. Similarly, any suitable R₄ can be added via the isonitrile route.

- 5 For instance, the preparation of 2-aminopyrimidin-4-yl imidazole compounds of Formula (I), when R₂ is a 4-substituted cyclohexyl moiety is illustrated in Scheme X. Condensation of the appropriate imine and isonitrile is carried out in a typical fashion. Once the relevant moiety is introduced at the 2-position of the pyrimidine ring, the ketone in the cyclohexyl ring can be unmasked and transformed to an alcohol or any
10 other suitable functionality via the corresponding epoxide.



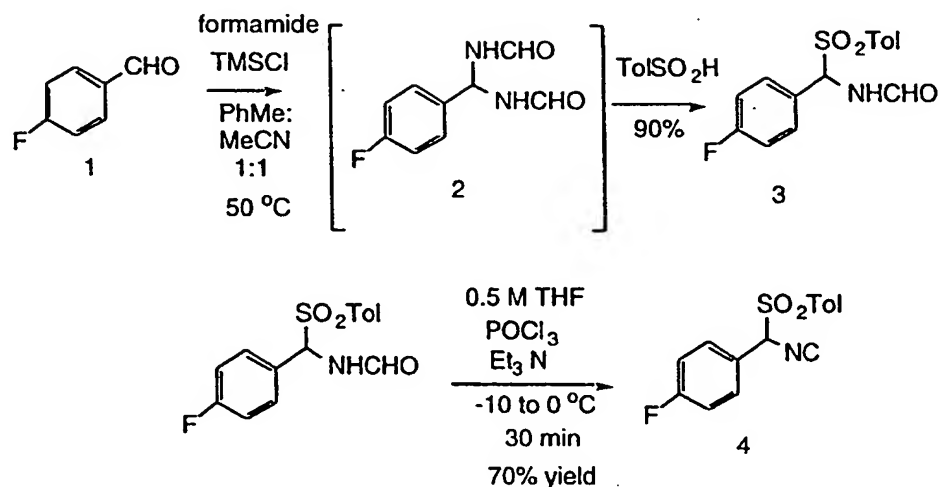
Scheme X

As illustrated in Scheme XI, the 2-aminopyridine containing compounds of formula I can be prepared by displacing the corresponding 2-chloropyridine precursor with the desired amine or its respective anion. Preparation of 2-chloropyridine-4-carboxaldehyde is also illustrated in Scheme XI. Imine formation and cycloaddition with isonitrile are conducted in the same manner as with the pyrimidine derivatives.



Scheme XI

An optimal method of making an isonitrile of Formula (II) is illustrated below, in Scheme XII.



5

SCHEME XII

The conversion of the substituted aldehyde to the tosylbenzyl formamide may be accomplished by heating the aldehyde, 1-Scheme XII, with an acid, such as p-toluenesulfonic acid, formic acid or camphorsulfonic acid; with formamide and p-toluenesulfonic acid [under reaction conditions of about 60°C for about 24 hours]. Preferably, no solvent is used. The reaction, may give poor yields (< 30%) when solvents, such as DMF, DMSO, toluene, acetonitrile, or excess formamide are used. Temperatures less than 60°C are generally poor at producing the desired product, and temperatures in excess of 60°C may produce a product which decomposes, or obtain a benzylic bis-formamide, 2-Scheme XI.

Another embodiment of the present invention is the synthesis of the tosyl benzyl formamide compound, achieved by reacting the bisformamide intermediate, 2-Scheme XI with p-toluenesulfonic acid. In this preferred route, preparation of the bis-formamide from the aldehyde is accomplished by heating the aldehyde with formamide, in a suitable solvent with acid catalysis. Suitable solvents are toluene, acetonitrile, DMF, and DMSO or mixtures thereof. Acid catalysts, are those well known in the art, and include but are not limited to hydrogen chloride, p-toluenesulfonic acid, camphorsulfonic acid, and other

anhydrous acids. The reaction can be conducted at temperatures ranging from about 25°C to 110°C, preferably about 50°C, suitably for about 4 to about 5 hours, longer reaction times are also acceptable. Product decomposition and lower yields may be observed at higher temperatures (>70°C) at prolonged reactions times. Complete
5 conversion of the product generally requires water removal from the reaction mixture.

Preferred conditions for converting a bis-formamide derivative to the tosyl benzyl formamide are accomplished by heating the bisformamide in a suitable solvent with an acid catalyst and p-toluenesulfinic acid. Solvents for use in this reaction include but are not limited to toluene, and acetonitrile or mixtures thereof. Additional mixtures of these
10 solvents with DMF, or DMSO may also be used but may result in lower yields. Temperatures may range from about 30°C to about 100°C. Temperatures lower than 40°C and higher than 60°C are not preferred as the yield and rate decreases. Preferably the range is from about 40 to 60°C, most preferably about 50°C. The optimal time is about 4 to 5 hours, although it may be longer. Preferably, acids used include but are not
15 limited to, toluenesulfonic acid, camphorsulfonic acid, and hydrogen chloride and other anhydrous acids. Most preferably the bisformamide is heated in toluene:acetonitrile in a 1:1 ratio, with p-toluenesulfinic acid and hydrogen chloride.

Another embodiment of the present invention is the preferred synthetic route for synthesis of the tosylbenzyl formamide compound which is accomplished using a one-
20 pot procedure. This process first converts the aldehyde to the bis-formamide derivative and subsequently reacts the bis-formamide derivative with toluenesulfinic acid. This procedure combines the optimized conditions into a single, efficient process. High yields, >90% of the aryl benzylformamide may be obtained in such a manner.

Preferred reaction conditions employ a catalyst, such as trimethylsilyl chloride (TMSCl), in a preferred solvent, toluene:acetonitrile, preferably in a 1:1 ratio. A
25 reagent, such as TMSCl, is preferred which reacts with water produced therein and at the same time produces hydrogen chloride to catalyze the reaction. Also preferred is use of hydrogen chloride and p-toluenesulfonic acid. Therefore, three suitable reaction conditions for use herein include 1) use of a dehydrating agent which also provides
30 hydrogen chloride, such as TMSCl; or by 2) use of a suitable dehydrating agent and a suitable source of acid source, such as but not limited to, camphorsulfonic acid,

hydrogen chloride or toluenesulfonic acid; and 3) alternative dehydrating conditions, such as the azeotropic removal of water, and using an acid catalyst and p-toluene sulfinic acid.

Compounds of the formula (II) where p is 2 may also be prepared by reacting in the presence of a strong base a compound of the formula (VI) -Scheme I, R_4CH_2NC with a compound of the formula (VII)-Scheme I, $ArSO_2L_1$ wherein R_4 and Ar are as defined herein and L_1 is a leaving group such as halo, e.g. fluoro. Suitable strong bases include, but are not limited to, alkyl lithiums such as butyl lithium or lithium diisopropylamide (Van Leusen *et al.*, Tetrahedron Letters, No. 23, 2367-68 (1972)).

10

The compounds of Formula (II), in Scheme I, may be prepared by the methods of van Leusen *et al.*, *supra*. For example a compound of the Formula (II) may be prepared by dehydrating a compound of the Formula (IV)-Scheme I, wherein Ar, R_4 and p are as defined herein.

15

Suitable dehydrating agents include phosphorus oxychloride, oxalyl chloride, thionyl chloride, phosgene, or tosyl chloride in the presence of a suitable base such as triethylamine or diisopropylethylamine, or similar bases, etc. such as pyridine. Suitable solvents are dimethoxy ether, tetrahydrofuran, or halogenated solvents, preferably THF. The reaction is most efficient when the reaction temperatures are kept between -10°C and 0°C . At lower temperatures incomplete reaction occurs and at higher temperatures, the solution turns dark and the product yield drops.

20

The compounds of formula (IV)-Scheme I may be prepared by reacting a compound of the formula (V)-Scheme I, R_4CHO where R_4 is as defined herein, with $ArS(O)_pH$ and formamide with or without water removal, preferably under dehydrating conditions, at ambient or elevated temperature e.g. 30° to 150° , conveniently at reflux, optionally in the presence of an acid catalyst. Alternatively trimethylsilylchloride can be used in place of the acid catalyst. Examples of acid catalysts include camphor-10-sulphonic acid, formic acid, p-toluenesulphonic acid, hydrogen chloride or sulphuric acid.

25

30

The compounds of formula (VI)-Scheme I may be prepared by reacting a compound of the formula (VIII)-Scheme I, $R_4CH_2NH_2$ with an alkyl formate (e.g.

ethylformate) to yield an intermediate amide which can be converted to the desired isonitrile by reacting with well known dehydrating agent, such as but not limited to oxalyl chloride, phosphorus oxychloride or tosyl chloride in the presence of a suitable base such as triethylamine.

- 5 Alternatively a compound of the formula (VIII) - Scheme I may be converted to a compound of the formula (VI) - Scheme I by reaction with chloroform and sodium hydroxide in aqueous dichloromethane under phase transfer catalysis.

The compounds of the formula (III) - Scheme I may be prepared by reacting a compound of the formula R_1CHO with a primary amine R_2NH_2 .

- 10 The amino compounds of the formula (VIII) - Scheme I are known or can be prepared from the corresponding alcohols, oximes or amides using standard functional group interconversions.

Suitable protecting groups for use with hydroxyl groups and the imidazole nitrogen are well known in the art and described in many references, for instance,

- 15 Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyldimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, $(CR_{10}R_{20})_n$. Suitable examples of imidazole nitrogen protecting groups include tetrahydropyranyl.

- 20 Pharmaceutically acid addition salts of compounds of Formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

METHODS OF TREATMENT

- 25 The compounds of Formula (I), or Formula (A), or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages.

- 30 For purposes herein in the Method of Treatment section, compounds of Formula (I) is used interchangeably with compounds of Formula (A). The methods of

formulation, dosage forms, disease management, etc. are the same for both formulas. For instance, "Compounds of Formula (I) are capable..." is also the same as stating : "Compounds of Formula (I) or Formula (A) are capable."

Compounds of Formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-6, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) are capable of inhibiting inducible proinflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGHS-2) and are therefore of use in therapy. These proinflammatory lipid mediators of the cyclooxygenase (CO) pathway are produced by the inducible COX-2 enzyme. Regulation, therefore of COX-2 which is responsible for the these products derived from arachidonic acid, such as prostaglandins affect a wide variety of cells and tissues are important and critical inflammatory mediators of a wide variety of disease states and conditions. Expression of COX-1 is not effected by compounds of Formula (I). This selective inhibition of COX-2 may alleviate or spare ulcerogenic liability associated with inhibition of COX-1 thereby inhibiting prostoglandins essential for cytoprotective effects. Thus inhibition of these pro-inflammatory mediators is of benefit in controlling, reducing and alleviating many of these disease states. Most notably these inflammatory mediators, in particular prostaglandins, have been implicated in pain, such as in the sensitization of pain receptors, or edema. This aspect of pain management therefore includes treatment of neuromuscular pain, headache, cancer pain, and arthritis pain. Compounds of Formula (I) or a pharmaceutically acceptable salt thereof, are of use in the prophylaxis or therapy in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

Accordingly, the present invention provides a method of inhibiting the synthesis of COX-2 which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The present invention also provides for a method of prophylaxis treatment in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

A new member of the MAP kinase family, alternatively termed CSBP, p38, or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors, of the present invention, compounds of Formula (I), have been determined to be potent and selective inhibitors of CSBP/p38/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the first time a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages.

The cytokine inhibitors were subsequently tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such *in vivo* studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of TNF correlated with survival and protection from endotoxic shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system. Griswold et al., (1988) *Arthritis Rheum.* 31:1406-1412; Badger, et al., (1989) *Circ. Shock* 27, 51-61; Votta et al., (1994) *in vitro. Bone* 15, 533-538; Lee et al., (1993). *B Ann. N. Y. Acad. Sci.* 696, 149-170.

Another aspect of the present invention, therefore, is the treatment of a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

Suitable diseases, include those mentioned herein for IL-1, IL-6, IL-8 and TNF and more specifically those disease which are CSBP/RK/p38 kinase mediated diseases. These include, but are not limited to rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injuries, such as neurotrauma and ischemia, including both open and closed head injuries), psoriasis, restenosis, such as occurs following coronary angioplasty, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption diseases, osteoporosis, , graft vs. host reaction, allograft rejections, Crohn's disease, ulcerative colitis or any other anti-inflammatory bowel disease (IBD), or pyresis.

CNS injuries as defined herein include both open or penetrating head trauma, such as by surgery, or a closed head trauma injury, such as by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area.

Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. The role of inflammatory cytokines in this are has been emerging and the present invention provides a mean for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available.

TNF- α is a cytokine with proinflammatory actions, including endothelial leukocyte adhesion molecule expression. Leukocytes infiltrate into ischemic brain lesions and hence compounds which inhibit or decrease levels of TNF would be useful for treatment of ischemic brain injury. See Liu et al., Stoke, Vol. 25., No. 7, pp 1481-88 (1994) whose disclosure is incorporated herein by reference.

Models of closed head injuries and treatment with mixed 5-LO/CO agents is discussed in Shohami et al., J. of Vasc & Clinical Physiology and Pharmacology, Vol. 3, No. 2, pp. 99-107 (1992) whose disclosure is incorporated herein by reference. Treatment which reduced edema formation was found to improve functional outcome in those animals treated.

In particular, compounds of Formula (I) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

Accordingly, in another aspect, this invention relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic β cells and Alzheimer's disease.

In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia

secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Compounds of Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of Formula (1). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

The compounds of Formula (I) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

Compounds of Formula (I) have also been shown to inhibit the production of IL-8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to a

method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

The discovery that the compounds of Formula (I) are inhibitors of cytokines, specifically IL-1, IL-6, IL-8 and TNF is based upon the effects of the compounds of Formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are described herein.

As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

- b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;
- c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a postranslational event; or
- 5 d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by

10 TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease stated mediated by TNF.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects

15 the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however

20 also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epideral keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- α)

25 and Tumor Necrosis Factor beta (TNF- β).

As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of Formula (I) which will cause a decrease

in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or

30 caused by, excessive or unregulated cytokine production.

As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

As TNF- β (also known as lymphotoxin) has close structural homology with TNF- α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be Formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or
5 diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary
10 widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I)
15 externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid
20 preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5%
25 w/w, more preferably from 0.1% to 1% w/w of the Formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an
30 agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100° C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation

administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.01 to about 80 mg/kg of total
5 body weight, preferably from about 0.1 to 30 mg/kg, more preferably from about 0.2 mg to 15mg. The daily parenteral dosage regimen about 0.01 to about 80 mg/kg of total body weight, preferably from about 0.1 to about 30 mg/kg, and more preferably from about 0.2 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily
10 inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being
15 treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

20 The novel compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of cytokine inhibition or production. In particular, cytokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section, but in particular viral infections. Examples
25 of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

The invention will now be described by reference to the following biological
30 examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds of the present invention were determined by the following *in vitro* assays:

5 Interleukin - 1 (IL-1)

Human peripheral blood monocytes are isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al*, J Immunol, 132, 936 (1984). These monocytes (1×10^6) are plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells are
10 allowed to adhere for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds are then added to the cells for 1h before the addition of lipopolysaccharide (50 ng/ml), and the cultures are incubated at 37°C for an additional 24h. At the end of this period, culture supernatants are removed and clarified of cells and all debris. Culture supernatants are then immediately assayed for IL-1 biological
15 activity, either by the method of Simon *et al.*, J. Immunol. Methods, 84, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, J. ImmunoTherapy, 6 (1), 1-12 (1990) (ELISA assay).

20 Tumour Necrosis Factor (TNF):

Human peripheral blood monocytes are isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. *et al.*, J Immunol, 132(2), 936 (1984). The monocytes are plated at a density of 1×10^6 cells/ml medium/well in 24-well multi-dishes. The cells are allowed to adhere for 1 hour
25 after which time the supernatant is aspirated and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells are incubated for 45 minutes in the presence or absence of a test compound at 1nM-10mM dose ranges (compounds are solubilized in dimethyl sulfoxide/ethanol, such that the final solvent concentration in
30 the culture medium is 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopolysaccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) is then added (100 ng/ml

in 10 ml phosphate buffered saline) and cultures incubated for 16-18 hours at 37°C in a 5% CO₂ incubator. At the end of the incubation period, culture supernatants are removed from the cells, centrifuged at 3000 rpm to remove cell debris. The supernatant is then assayed for TNF activity using either a radio-immuno or an ELISA assay, as
5 described in WO 92/10190 and by Becker *et al.*, J Immunol, 1991, 147, 4307.

IL-1 and TNF inhibitory activity does not seem to correlate with the property of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition. Further the ability to inhibit production of prostaglandin and/or leukotriene synthesis, by
10 nonsteroidal anti-inflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity does not mean that the compound will necessarily also inhibit TNF or IL-1 production, at non-toxic doses.

Interleukin -8 (IL-8):

15 Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells are then diluted 20-fold before being plated (250µl) into gelating coated 96-well plates. Prior to use, culture medium are replaced with fresh medium (200µl). Buffer or test compound (25µl, at
20 concentrations between 1 and 10µM) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO₂. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard
25 curve. IC₅₀'s where appropriate are generated by non-linear regression analysis.

Cytokine Specific Binding Protein Assay

A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over
30 the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay.

the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible cytokine inhibitor binding assay was developed using soluble cytosolic fraction from THP.1 cells and a radiolabeled compound. Patent Application USSN 08/123175 Lee et al., filed September 1993, USSN; Lee et al., PCT 5 94/10529 filed 16 September 1994 and Lee et al., *Nature* 300, n(72), 739-746 (Dec. 1994) whose disclosures are incorporated by reference herein in its entirety describes the above noted method for screening drugs to identify compounds which interact with and bind to the cytokine specific binding protein (hereinafter CSBP). However, for purposes 10 or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the CSBP may be employed in the screening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein 15 complex and compound capable of forming, enhancing or interfering with said complexes are detected.

Representative compounds of Formula (I), Examples 2 to 28, have all demonstrated positive inhibitory activity in this binding assay.

20 **Prostaglandin endoperoxide synthase-2 (PGHS-2) assay:**

The following assay describes a method for determining the inhibitory effects of compounds of Formula (I) on human PGHS-2 protein expression in LPS stimulated human monocytes.

Method: Human peripheral blood monocytes were isolated from buffy coats by 25 centrifugation through Ficoll and Percoll gradients. Cells were seeded at 2×10^6 /well in 24 well plates and allowed to adhere for 1 hour in RPMI supplemented with 1% human AB serum, 20mM L-glutamine, Penicillin-Streptomycin and 10mM HEPES. Compounds were added at various concentrations and incubated at 37°C for 10 minutes. LPS was added at 50 ng/well (to induce enzyme expression) and incubated overnight at 30 37°C. The supernatant was removed and cells washed once in cold PBS. The cells were lysed in 100µl of cold lysis buffer(50mM Tris/HCl pH 7.5, 150mM NaCl, 1% NP40,

0.5% sodium deoxycholate, 0.1% SDS, 300ug/ml DNase, 0.1% TRITON X-100, 1mM PMSE, 1mM leupeptin, 1mM pepstatin). The lysate was centrifuged (10,000 X g for 10 min. at 4°C) to remove debris and the soluble fraction was subjected to SDS PAGE analysis (12% gel). Protein separated on the gel were transferred onto nitrocellulose membrane by electrophoretic means for 2 hours at 60 volts. The membrane was pretreated for one hour in PBS/0.1% Tween 20 with 5% non-fat dry milk. After washing 3 times in PBS/Tween buffer, the membrane was incubated with a 1:2000 dilution of a monospecific antiserum to PGHS-2 or a 1:1000 dilution of an antiserum to PGHS-1 in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was washed 3X in PBS/Tween and then incubated with a 1:3000 dilution of horseradish peroxidase conjugated donkey antiserum to rabbit Ig (Amersham) in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was then washed 3X in PBS/Tween and the ECL immunodetection system (Amersham) was used to detect the level of expression of prostaglandin endoperoxide synthases-2.

15 Results: The following compounds were tested and found to be active in this assay (i.e., inhibited LPS induced PGHS-2 protein expression in rank order potency similar to that for inhibiting cytokine production as noted in assays indicated): 6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo[2,1-b]thiazole; and Dexamethasone

20 Several compounds were tested and found to be inactive (up to 10uM): 2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-(5H)-pyrrolo[1,2-a]imidazole; rolipram ; phenidone and NDGA. None of these compounds tested were found to inhibit PGHS-1 or cPLA₂ protein levels in similar experiments.

TNF- α in Traumatic Brain Injury Assay

25 The present assay provides for examination of the expression of tumor necrosis factor mRNA in specific brain regions which follow experimentally induced lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) are anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left

30 temporoparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury, n=18). Animals are sacrificed by decapitation at 1, 6 and 24 hr. post injury.

brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured parietal cortex (LA), corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) are prepared. Total RNA is isolated and Northern blot

5 hybridization is performed and quantitated relative to an TNF- α positive control RNA (macrophage = 100%). A marked increase of TNF- α mRNA expression is observed in LH ($104 \pm 17\%$ of positive control, $p < 0.05$ compared with sham), LC ($105 \pm 21\%$, $p < 0.05$) and LA ($69 \pm 8\%$, $p < 0.01$) in the traumatized hemisphere 1 hr. following injury. An increased TNF- α mRNA expression is also observed in LH ($46 \pm 8\%$, $p < 0.05$), LC

10 ($30 \pm 3\%$, $p < 0.01$) and LA ($32 \pm 3\%$, $p < 0.01$) at 6 hr. which resolves by 24 hr. following injury. In the contralateral hemisphere, expression of TNF- α mRNA is increased in RH ($46 \pm 2\%$, $p < 0.01$), RC ($4 \pm 3\%$) and RA ($22 \pm 8\%$) at 1 hr. and in RH ($28 \pm 11\%$), RC ($7 \pm 5\%$) and RA ($26 \pm 6\%$, $p < 0.05$) at 6 hr. but not at 24 hr. following injury. In sham (surgery without injury) or naive animals, no consistent changes in expression of TNF- α

15 mRNA is observed in any of the 6 brain areas in either hemisphere at any times. These results indicate that following parasagittal fluid-percussion brain injury, the temporal expression of TNF- α mRNA is altered in specific brain regions, including those of the non-traumatized hemisphere. Since TNF- α is able to induce nerve growth factor (NGF) and stimulate the release of other cytokines from activated astrocytes, this post-traumatic

20 alteration in gene expression of TNF- α plays an important role in both the acute and regenerative response to CNS trauma.

CNS Injury model for IL- β mRNA

This assay characterizes the regional expression of interleukin-1 β (IL-1 β) mRNA in

25 specific brain regions following experimental lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats ($n=42$) are anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left temporoparietal cortex ($n=18$), or "sham" treatment (anesthesia and surgery without injury). Animals are sacrificed at 1, 6

30 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured

parietal cortex (LA), corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) were prepared. Total RNA is isolated and Northern blot hybridization is performed and the quantity of brain tissue IL-1 β mRNA is presented as percent relative radioactivity of IL-1 β positive macrophage RNA which is loaded on same gel. At 1 hr. following brain injury, a marked and significant increase in expression of IL-1 β mRNA is observed in LC (20.0 \pm 0.7% of positive control, n=6, p < 0.05 compared with sham animal), LH (24.5 \pm 0.9%, p < 0.05) and LA (21.5 \pm 3.1%, p < 0.05) in the injured hemisphere, which remained elevated up to 6 hr. post injury in the LC (4.0 \pm 0.4%, n=6, p < 0.05) and LH (5.0 \pm 1.3%, p < 0.05). In sham or naive animals, no expression of IL-1 β mRNA is observed in any of the respective brain areas. These results indicate that following TBI, the temporal expression of IL-1 β mRNA is regionally stimulated in specific brain regions. These regional changes in cytokines, such as IL-1 β play a role in the post-traumatic pathologic or regenerative sequelae of brain injury.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon atmosphere unless otherwise indicated.

In the Examples, all temperatures are in degrees Centigrade ($^{\circ}$ C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated. 1 H-NMR (hereinafter "NMR") spectra were recorded at 250 MHz using a Bruker AM 250 or Am 400 spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

Flash Chromatography is run over a Merck Silica gel 60 (230-400 mesh).

Example 1

2-Methylthiopyrimidine-4-carboxaldehyde

- a) 2-Methylthiopyrimidine-4-carboxaldehyde dimethyl acetal. Pyruvaldehyde dimethyl acetal (19.2 mL, 159.1 mmol) and N,N-dimethylformamide dimethyl acetal (21.12 mL, 159.1 mmol) were combined in a 500 mL flask. After heating at 100 °C 4.5 h, thiourea (11.0 g, 144.5 mmol), NaOMe (25 wt. % solution in MeOH, 39.7 mL, 173 mmol) and 30 mL of MeOH were added and heating was continued at 65 °C. After 18 h, the solution was cooled to 25 °C and MeI (10.8 mL, 173 mmol) was added over 5 min (exothermic). After 3 h, the solution was diluted with 250 mL of H₂O and extracted with EtOAc (3 X 100 mL). The organics were combined, dried (Na₂SO₄) and concentrated to give the title compound (26.8 g, 93%) as a brown oil.
- b) 2-Methylthiopyrimidine-4-carboxaldehyde. 2-Methylthiopyrimidine-4-carboxaldehyde dimethyl acetal (25 g, 125 mmol) and 3 N HCl were heated to 40 °C for 18 h. The reaction mixture was cooled to ambient temperature and neutralized by addition of solid NaHCO₃ and extracted with EtOAc (5 X 500 mL). The combined extracts were dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography eluting with dichloromethane to afford the title compound as an off-white solid; yield 12 g (62 %). ¹H NMR (CDCl₃) δ 9.95 (s, 1H), 8.77 (d, 1H), 7.43 (d, 1H), 2.63 (s, 3H); or
- c) 2-Methylthiopyrimidine-4-carboxaldehyde. 2-Methylthiopyrimidine-4-carboxaldehyde dimethyl acetal (30.0 g, 150 mmol) was dissolved in 300 mL of glacial AcOH and 3 mL of conc H₂SO₄ and heated at 80 °C. After 10 h, the solution was cooled to 25 °C and the AcOH was removed *in vacuo*. The residue was diluted in 200 mL of CH₂Cl₂ and washed with saturated NaHCO₃ (3 X 50 mL), H₂O (50 mL) and brine (50 mL). The organics were dried (MgSO₄) and concentrated to give the title compound as a brown oil; yield 22.1 g (96%); or
- d) 2-Methylthiopyrimidine-4-carboxaldehyde monomethyl-monoacetyl acetal. Concentrated H₂SO₄ (2 mL) was added to a solution of 2-methylthiopyrimidine-4-carboxaldehyde dimethyl acetal (78 g, .39 mol) in Ac₂O (105 mL) and the reaction mixture was heated to reflux for 3 h. After cooling to ambient temperature, the solvent was evaporated under reduced pressure. The residue was slurried with EtOAc and filtered. The filtrate was evaporated to afford the title compound as a brown oil; yield 78

g (88%): ^1H NMR (CDCl_3) δ 8.60 (d, 1H), 7.15 (d, 1H), 6.50 (s, 1H), 3.60 (s, 3H), 2.60 (s, 3H), 2.20 (s, 3H).

e) 2-Methylthiopyrimidine-4-carboxaldehyde. To a solution of 2-methylthiopyrimidine-4-carboxaldehyde monomethyl-monoacetyl acetal (53 g, 0.23 mol) was added NaOMe (5.5 g, 0.098 mol). The reaction mixture was stirred at ambient temperature for 3 h. The solvent was evaporated under reduced pressure and the residue partitioned between EtOAc and H_2O . The aqueous phase was extracted 4 X with EtOAc and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The residue was subjected to flash chromatography eluting with 50% EtOAc in hexanes to afford the title compound as an off-white solid; yield 33 g (91%).

f) 2-Methylthiopyrimidine-4-carboxaldehyde
A solution of 2-methylthiopyrimidine-4-carboxaldehyde monomethyl-monoacetyl acetal (46 g, 0.20 mol) in conc HCl (6 mL) was stirred at ambient temperature for 24 h. The reaction mixture was carefully neutralized with sat aq NaHCO_3 and extracted with EtOAc. The organic phase was washed with brine, dried (MgSO_4) and evaporated under reduced pressure. The residue was passed through a pad of silica gel eluting with 20% EtOAc/hexanes to afford the title compound as a white solid in 90% yield.

Example 2

20 5-[(2-Benzylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole

a) 2-Methylthiopyrimidine-4-carboxaldehyde (1-methylpiperidin-4-yl)imine
2-Methylthiopyrimidine-4-carboxaldehyde (5.6 g, 36 mmol) and 4-amino-1-methylpiperidine dihydrochloride (6.73 g, 36 mmol) were dissolved in 200 mL of CH_2Cl_2 and NaHCO_3 (10.6 g, 126 mmol) was added. After 20 h, the solution was filtered and concentrated to yield 8.9 g (98%) of the title compound as a brown oil.

b) 4-Fluorophenyl-tolylsulfonmethylformamide
To a suspension of p-toluenesulfonic acid sodium salt (30 g) in H_2O (100 mL) was added methyl t-butyl ether (50 mL) followed by dropwise addition of conc HCl (15 mL). After stirring 5 min, the organic phase was removed and the aqueous phase was extracted with methyl t-butyl ether. The organic phase was dried (Na_2SO_4) and concentrated to near

dryness. Hexane was added and the resulting precipitate collected to afford p-toluenesulfinic acid; yield 22 g.

p-Toluenesulfinic acid (22 g, 140.6 mmol), p-fluorobenzaldehyde (22 mL, 206 mmol), formamide (20 mL, 503 mmol) and camphor sulphonic acid (4 g, 17.3 mmol) were
5 combined and stirred at 60 °C 18 h. The resulting solid was broken up and stirred with a mixture of MeOH (35 mL) and hexane (82 mL) then filtered. The solid was resuspended in MeOH / hexanes (1:3, 200 mL) and stirred vigorously to break up the remaining
chunks. Filtration afforded the title compound (27 g, 62 % yield): ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.71 (d, 2H), 7.43 (dd, 2H), 7.32 (d, 2H), 7.08 (t, 2H), 6.34 (d,
10 1H), 2.45 (s, 3H).

c) 4-Fluorophenyl-tolylsulfonmethylisocyanide

4-Fluorophenyl-tolylsulfonmethylformamide (2.01g, 6.25 mmol) in DME (32 mL) was cooled to -10 °C. POCl₃ (1.52 mL, 16.3 mmol) was added followed by the dropwise addition of triethylamine (4.6 mL, 32.6 mmol) in DME (3mL) keeping the internal
15 temperature below -5 °C. The mixture was gradually warmed to ambient temperature over 1 h., poured into H₂O and extracted with EtOAc. The organic phase was washed with sat aq NaHCO₃, dried (Na₂SO₄), and concentrated. The resulting residue was triturated with petroleum ether and filtered to afford the title compound (1.7 g, 90%
yield): ¹H NMR (CDCl₃) δ 7.63 (d, 2H), 7.33 (m, 4H), 7.10 (t, 2H), 5.60 (s, 1H), 2.50
20 (s, 3H).

d) 4-(Fluorophenyl)-1-(methyl-4-piperidiny)-5-(2-methylthio-4-pyrimidinyl)imidazole

t-BuNH₂ (3.90 mL, 37.08 mmol) was added rapidly to a solution of 2-methylthiopyrimidine-4-carboxaldehyde (1-methylpiperdin-4-yl)imine (3.71 g, 14.83
25 mmol) and 4-fluorophenyl-tosylmethylisocyanide (5.15 g, 17.8 mmol) dissolved in 50 mL of DME at 25 °C. After 14 h, the solution was diluted with 50 mL of EtOAc and washed with 50 mL of sat aq NaHCO₃ and brine (25 mL). The organic phase was dried (Na₂SO₄) and concentrated. Crystallization of the crude residue from EtOAc/hexanes
afforded the title compound as light brown crystals; yield 2.85 g (50%): ¹H NMR
30 (CDCl₃, 300 MHz) δ 8.31 (1H, d, J = 5.1 Hz), 7.78 (1H, s), 7.40 (2H, m), 6.99 (2H, t, J

= 8.7 Hz), 6.76 (1H, d, J = 5.2 Hz), 4.67 (1H, m), 2.97 (2H, m), 2.58 (3H, s), 2.31 (3H, s), 2.06 (6H, m).

e) 4-(Fluorophenyl)-1-(methyl-4-piperidiny)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole

- 5 Potassium persulfate (3.2 g, 7.0 mmol) in water (75 mL) was added to a solution of 4-(fluorophenyl)-1-(methyl-4-piperidiny)-5-(2-methylthio-4-pyrimidinyl)imidazole (2.7 g, 7.0 mmol) in glacial AcOH (150 mL). After stirring at ambient temperature for 72 h, the reaction mixture was neutralized by the portion-wise addition of conc aq NH₄OH and extracted with CH₂Cl₂. The organic extract was washed with brine, dried
- 10 (MgSO₄) and concentrated. The residue was triturated with Et₂O to afford the title compound as an off-white solid; yield 2.3 g (83%).
- f) 5-[(2-Benzylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole
- 4-(Fluorophenyl)-1-(methyl-4-piperidiny)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole
- 15 (0.25 g, 0.63 mmol) and benzylamine (1.0 mL) were heated to 120 °C for 18 h. The reaction mixture was cooled to ambient temperature and triturated with ether to afford the title compound as an off-white solid; yield 0.23 g (82 %): ESMS *m/z* = 443 (M⁺ + H).

Example 3

- 20 4-(4-Fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-[2-(4-tetrahydrothio-pyran-2-yl)aminopyrimidin-4-yl]imidazole Following the procedure of example 2(f) except substituting 4-amino-tetrahydrothiopyran for benzylamine afforded the title compound as a tan solid in 19% yield: ESMS *m/z* = 453 (M⁺ + H).

Example 4

- 25 4-(4-Fluorophenyl)-5-[(2-hydroxy)ethylaminolpyrimidin-4-yl]-1-(1-methyl-piperidin-4-yl)imidazole
- A mixture of ethanolamine (2 mL) and 4-(fluorophenyl)-1-(methyl-4-piperidiny)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole were heated to 120 °C for 18 h. After cooling to
- 30 ambient temperature, the reaction mixture was poured into water and the resulting

precipitate collected, washed with H₂O and dried *in vacuo* to afford the title compound as an off-white solid; yield 0.19 g (64%): ESMS m/z = 397 (M^+ + H).

Example 5

5 5-[(2-(3-Chlorobenzylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)]imidazole

A mixture of 3-chlorobenzylamine (2 ml) and 4-(fluorophenyl)-1-(methyl-4-piperidinyl)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole (0.20g, 0.50 mmol) was heated to 120 °C for 18 h. After cooling to ambient temperature, the reaction mixture was
10 concentrated and the residue was subjected to column chromatography on silica gel. Successive elution with EtOAc and 20% MeOH in CH₂Cl₂ afforded the title compound (0.160 g, 67%) as white solid, mp = 199-201°C.

Example 6

15 5-[(2-(1-Naphthylmethylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)]imidazole Following the procedure of example 5 except substituting 1-naphthylmethylamine for 3-chlorobenzylamine afforded the title compound as an off-white solid in 49% yield: mp = 215-216 °C.

Example 7

20 5-[(2-(1-Benzyl-4-piperidinylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)]imidazole Following the procedure of example 5 except substituting 4-amino-1-benzylpiperidine for 3-chlorobenzylamine afforded the title compound as an off-white solid in 59% yield: ESMS m/z = 526 (M^+ + H).

Example 8

25 4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-[2-[3-(morpholino)propyl]-aminopyrimidin-4-yl]imidazole
Following the procedure of example 2(f) except substituting 4-(3-aminopropyl)morpholine for benzylamine afforded the title compound as a tan solid in
30 55% yield: ESMS m/z = 480 (M^+ + H).

Example 9

5-[(2-(Piperonylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)]imidazole

- 5 Following the procedure of example 5 except substituting Piperonylamine for 3-chlorobenzylamine afforded the title compound as an off-white solid in 55% yield: ESMS $m/z = 526 (M^+ + H)$.

Example 10

- 10 5-[(2-(5-Chlorotryptamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)]imidazole

A solution of 4-(fluorophenyl)-1-(methyl-4-piperidiny)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole (0.20 g, 0.50 mmol) and 5-chlorotryptamine (0.17 g, 0.60 mol) in DMF (15 mL) was heated for 18 h at 110 °C. After cooling to ambient temperature, the
15 solvent was evaporated under reduced pressure. The residue was subjected to flash chromatography eluting with 10 % methanol in CH₂Cl₂ followed by recrystallization from EtOAc / hexanes to afford the title compound; yield 0.061 g (23%): ESMS $m/z = 530 (M^+ + H)$.

Example 11

- 20 5-[(2-[(1-Ethoxycarbonyl)piperdin-4-yl]aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)]imidazole

Following the procedure of example 5 except substituting 4-amino-1-(ethoxycarbonyl)-piperidine afforded the title compound as a white solid in 70% yield: mp = 130-132 °C.

25

Example 12

5-[(2-(4-Piperidinylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)]imidazole

- A mixture of 5-[(2-(1-benzyl-4-piperidinylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)]imidazole (0.50 g, 0.95 mmol) and 10% palladium on carbon (10
30 %) was stirred under an atmosphere of H₂ for 18 h. The catalyst was removed by

filtration and the filtrate was evaporated under reduced pressure. The residue was recrystallized from EtOAc / hexanes to afford the title compound as a white solid; yield 0.98 g (24%); mp = 201-203 °C.

Example 13

5 5-[(2-(2,2,6,6-tetramethylpiperidin-4-yl)aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)]imidazole

Following the procedure of example 5 except substituting 4-amino-2,2,6,6-tetramethylpiperidine for 3-chlorobenzylamine afforded the title compound as a white solid in 74% yield; mp = 101-102 °C.

10

Example 14

4-(4-Fluorophenyl)-5-[2-(2-hydroxy)ethylaminopyrimidin-4-yl]-1-(2,2,6,6-tetramethylpiperidin-4-yl)-imidazole

15 a) 4-(4-Fluorophenyl)-5-[4-(2-methylsulfinyl)pyrimidinyl]-1-(2,2,6,6-tetramethylpiperidin-4-yl)imidazole

Following the procedure of Example 19 (c) except substituting 4-(4-fluorophenyl)-5-[4-(2-methylthio)pyrimidinyl]-1-(2,2,6,6-tetramethylpiperidin-4-yl)imidazole (prepared in example 17b) for 5-(2-methylthio-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-t-butoxycarbonyl)-4-piperidinyl]imidazole afforded the title compound as yellow foam in 53% yield.

20 b) 4-(4-Fluorophenyl)-5-[2-(2-hydroxy)ethylaminopyrimidin-4-yl]-1-(2,2,6,6-tetramethylpiperidin-4-yl)-imidazole

4-(4-Fluorophenyl)-5-[4-(2-methylsulfinyl)pyrimidinyl]-1-(2,2,6,6-tetramethylpiperidin-4-yl)imidazole (0.25 g, 0.57 mmol) and ethanolamine were heated to 120 °C for 18 h. Excess ethanolamine was removed by evaporation under reduced pressure and the residue was poured into sat aq NaHCO₃. The resulting precipitate was collected, washed with water, air-dried and triturated with ether to afford the title compound as a white solid in 60% yield. ESMS *m/z* = 439 (M⁺ + H).

30

Example 15

5-[2[(3-Bromophenyl)amino]pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole

Trimethylaluminum (2M in toluene, 2.9 mL, 5.8 mmol) was added to a stirred solution of 3-bromoaniline (1.0 g, 5.8 mmol) in toluene (25 mL) at ambient temperature. Stirring was continued until gas evolution ceased (~ 0.5 h) and 4-(fluorophenyl)-1-(methyl-4-piperidinyl)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole (0.58 g, 1.9 mmol) was added.

5 The resulting solution was heated to reflux for 0.5 h, cooled to ambient temperature and poured into a slurry of silica gel in CHCl_3 . The solids were removed by filtration and washed with 10% MeOH in CH_2Cl_2 . The combined filtrates were concentrated and the residue was purified by flash chromatography eluting with 10% MeOH in CH_2Cl_2 to afford the title compound as a white solid; yield 0.50 g (52%); ESMS $m/z = 507$ ($\text{M}^+ + \text{H}$).

10 H).

Example 16

4-(4-Fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-[(2-phenylamino)pyrimidin-4-yl]imidazole Using the procedure of Example 15 except substituting aniline for 3-bromoaniline afforded the title compound as a white solid in 37% yield. ESMS $m/z = 429$ ($\text{M}^+ + \text{H}$).

15

Example 17

4-(4-Fluorophenyl)-1-(2,2,6,6-tetramethylpiperidin-4-yl) 5-[(2-phenylamino)-pyrimidin-4-yl]imidazole

20

a) 2-Methylthiopyrimidine-4-carboxaldehyde(4-amino-2,2,6,6-tetramethylpiperidine)imine

A mixture of 4-amino-2,2,6,6-tetramethylpiperidine and 2-methylthiopyrimidine-4-carboxaldehyde were stirred in DMF to afford the title compound which was used without further purification.

25

b) 4-(4-Fluorophenyl)-5-[4-(2-methylthio)pyrimidinyl]-1-(2,2,6,6-tetramethylpiperidin-4-yl)imidazole

Following the procedure of Example 18(d) except substituting 2-methylthiopyrimidine-4-carboxaldehyde(4-amino-2,2,6,6-tetramethylpiperidine)imine for 2-N-methylamino-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine afforded the title compound as a light yellow solid in 64% yield.

30

c) 4-(4-Fluorophenyl)-5-[4-(2-methylsulfonyl)pyrimidinyl]-1-(2,2,6,6-tetramethylpiperdin-4-yl)imidazole

4-(4-Fluorophenyl)-5-[4-(2-methylthio)pyrimidinyl]-1-(2,2,6,6-tetramethylpiperdin-4-yl)imidazole (1.2 g, 2.8 mmol) was dissolved in methanol (11 mL) and cooled to 4 °C. Oxone (5.2 g, 8.5 mmol) in water (11 mL) was added and the reaction mixture was warmed to 23 °C. The reaction was stirred at this temperature for 1.75 h, poured into 10% aqueous sodium hydroxide (50 mL) and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with 10% aq NaOH, dried (K₂CO₃) and evaporated. Flash chromatography of the residue (0-8% MeOH in CH₂Cl₂) afforded the title compound in 72% yield.

d) 4-(4-Fluorophenyl)-1-(2,2,6,6-tetramethylpiperdin-4-yl)-5-[(2-phenyl)amino]pyrimidin-4-yl]-imidazole

Following the procedure of Example 15 except substituting 4-(4-fluorophenyl)-5-[4-(2-methylsulfonyl)pyrimidinyl]-1-(2,2,6,6-tetramethylpiperdin-4-yl)imidazole for 4-(fluorophenyl)-1-(methyl-4-piperdiny)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole and heating the reaction to 80 °C for 4 h instead of stirring at ambient temperature for 3 h afforded the title compound in 72% yield. ESMS m/z = 471 (M⁺ + H).

Example 18

20 5-[2-(Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-oxocyclohexyl)imidazole

a) 4-(1,3-Dioxycyclopentyl)-cyclohexanone oxime To a mixture of 1,4-cyclohexanedione monoethylene ketal (27.6 g, 177 mmol) and hydroxylamine hydrochloride (49.2 g, 708 mmol) in H₂O (250 mL) was added portionwise Na₂CO₃ (49.2 g, 547 mmol). After stirring 1 h, the mixture was extracted with EtOAc. The organic phase was dried (Na₂SO₄) and concentrated affording the title compound; yield 27.5 g.

b) 1-Amino-4-(1,3-dioxycyclopentyl)cyclohexane 4-(1,3-Dioxycyclopentyl)-cyclohexanone oxime (27.5 g, 161 mmol), Raney Ni (ca 13.5 mL as a suspension in EtOH) and EtOH (200 mL) were combined and shaken at 50 psi H₂ for 4 h. The catalyst was filtered off and the filtrate was concentrated to afford the title compound as a colorless oil (23.6 g, 93%): ¹H NMR (CDCl₃) δ 2.64 (m, 1H), 1.75 - 1.25 (m, 12 H).

c) 2-Methylthiopyrimidine-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine

Following the procedure of example 19(a) except using 1-amino-4-(1,3-dioxycyclopentyl) instead of 1-t-butoxycarbonyl-4-aminopiperidine afforded the title compound: $^1\text{H NMR}$ (CDCl_3) δ 8.51 (d, 1H), 8.21 (s, 1H), 7.53 (d, 1H), 3.93, (s, 4H),
5 3.40 (m, 1H), 2.55 (s, 3H), 1.94 - 1.70 (m, 6H), 1.61 (m, 2H).

d) 5-[4-(2-Methylthio)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-ethylene ketal cyclohexyl)imidazole

To a mixture of 2-methylthiopyrimidine-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine (2.0g, 6.8mmol) in DMF (10mL) was added 4-fluorophenyl-
10 toluenesulfonylmethylisocyanide (1.96g, 6.8mmol) and K_2CO_3 (1.18g, 8.57mmol) at 0 $^\circ\text{C}$. The mixture was stirred at 0 $^\circ\text{C}$ for 3h then at room temperature for 18h. EtOAc was added and the reaction mixture was filtered. The filtrate was washed with brine, dried and concentrated to near dryness. The resulting crystals were collected and washed with EtOAc/hexane (1:1) to afford the title compound as a pale yellow solid (1.77g, 61%):
15 $^1\text{H NMR}$ (CDCl_3) δ 8.33 (d, 1H), 7.81 (s, 1H), 7.43 (q, 2H), 7.12 (t, 2H), 6.78 (d, 1H), 4.74 (m, 1H), 4.00 (s, 4H), 2.59 (s, 3H), 2.18 (dd, 2H), 2.04 (dq, 2H), 1.89 (dd, 2H), 1.70 (dt, 2H).

e) 5-[4-(2-Methylsulfoxy)pyrimidinyl]-4-(4-fluorophenyl)-1-ethylene ketal cyclohexyl)imidazole

To a solution of the compound from the previous step (0.20 g, 0.48 mmol) in THF (2 mL) and MeOH (1 mL) at $^\circ\text{C}$ was added oxone monopersulfate (0.36 g, 0.56 mmol) dissolved in H_2O (2 mL). The mixture was stirred for 0.5 h. then poured into 10% NaOH and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated. The residue was triturated with Et_2O and filtered affording the title
25 compound as a white solid (0.089 g, 45% yield): $^1\text{H NMR}$ (CDCl_3) δ 8.36 (d, 1H), 7.82 (s, 1H), 7.42 (q, 2H), 7.02 (t, 2H), 6.79 (d, 1H), 4.80 (m, 1H), 4.00 (s, 3H), 2.20 (m, 2H), 2.06 (m, 3H), 1.89 (m, 2H), 1.70 (m, 5H).

f) 5-[2-(Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-ethylene ketal cyclohexyl)imidazole

30 Following the procedure of Example 16 except substituting 5-[4-(2-methylsulfinyl)pyrimidinyl]-4-(4-fluorophenyl)-1-ethylene ketal cyclohexyl)imidazole

for 4-(fluorophenyl)-1-(methyl-4-piperidinyl)-5-(2-methylsulfinyl-4-pyrimidinyl)imidazole afforded the title compound as a yellow solid (0.358 g, 45% yield): ¹H NMR (CDCl₃) δ 8.30 (d, 1H), 7.80 (s, 1H), 7.62 (d, 2H), 7.50 (q, 2H), 7.36 (t, 2H), 7.09 (t, 1H), 7.03 (t, 2H), 6.61 (d, 1H), 4.70 (m, 1H), 3.98 (m, 4H), 2.05 (m, 4H), 1.75 (m, 2H), 1.45 (m, 2H).

h) 5-[2-(Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-oxocyclohexyl)imidazole

A suspension of 5-[2-(phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-ethylene ketal cyclohexyl)imidazole (0.35g, 0.76mmol) in 3N HCl (4.5mL) was stirred for 3h, cooled to 0°C and neutralized with sat aq NaHCO₃. The mixture was extracted with EtOAc and dried. Evaporation of the solvent afforded the title compound: mp 205-207 °C.

Example 19

15 4-(4-Fluorophenyl)-5-[2-(phenylamino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole

a) 2-Methylthiopyrimidine-4-carboxaldehyde [1-t-butoxycarbonyl-4-aminopiperidine] imine

2-Methylthiopyrimidine-4-carboxaldehyde (1.51g, 9.8 mmol), 1-t-butoxycarbonyl-4-aminopiperidine (Mach R. H., *et al.*, *J. Med. Chem.* 1993 36, 3707) (2.1 g, 10.5 mmol), MgSO₄ (ca 2 g) and CH₂Cl₂ (75 mL) were combined and stirred at 23 °C for 16 h. Filtration and concentration of the filtrate afforded the title compound as a yellow oil: ¹H NMR (CDCl₃) δ 8.57 (d, 1), 8.27 (s, 1), 7.58 (d, 1), 4.05 (m, 2), 3.55 (m, 1), 3.00 (m, 2), 2.60 (s, 3), 1.75 (m, 4), 1.48 (s, 9).

b) 5-(2-Methylthio-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-t-butoxycarbonyl)-4-piperidinyl]imidazole

Following the procedure of Example 18 (d) except substituting 2-methylthiopyrimidine-4-carboxaldehyde [1-t-butoxycarbonyl-4-aminopiperidine] imine for 2-methylthiopyrimidine-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine afforded the title compound as a brown solid in 50 % yield: ESMS *m/z* = 470 (M⁺ + H).

30 c) 5-(2-Methylsulfinyl-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-t-butoxycarbonyl)-4-piperidinyl]imidazole

5-(2-Methylthio-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-t-butoxycarbonyl)-4-piperidinyl]imidazole (4.69 g, 10 mmol) was dissolved in THF, cooled to -10 °C and oxone (6.14g) in H₂O (50 mL) was added dropwise (T < 5°). The resulting mixture was warmed to 20 °C over ca 50 min, poured into a vigorously stirred mixture of 10% aq NaOH (300 mL), ice (100 mL), and EtOAc (300 mL). The phases were separated, the organic phase was dried (Na₂SO₄), and concentrated to give a yellow oil. Flash chromatography (0-2% MeOH in CH₂Cl₂) afforded the title compound; yield 3.58g (74%); ESMS *m/z* = 486 (M⁺ + H).

d) 4-(4-Fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperidin-4-yl]imidazole

Following the procedure of 16 except substituting 5-(2-methylsulfinyl-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-t-butoxycarbonyl)-4-piperidinyl]imidazole for 4-(4-fluorophenyl)-1-[(1-methyl)piperidin-4-yl]-5-[(2-methylsulfinyl) pyrimidin-4-yl]imidazole afforded the title compound as a white solid in 40% yield.

e) 4-(4-Fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole

HCL (4M in dioxane, 10 mL) was added to 4-(4-fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperidin-4-yl]imidazole (1.0 g, 19 mmol) at ambient temperature. After stirring for 15 min at ambient temperature, the reaction mixture was partially neutralized with 10% aq NaOH followed by sat aq NaHCO₃. The neutralized mixture was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Trituration with ether afforded the title compound as a white solid in 74% yield. ESMS *m/z* = 415 (M⁺ + H).

Example 20

4-(4-Fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole

a) 1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole

To a solution of pyruvaldehyde (40% w/w solution in water, 6.6 mL, 7.8 g, 0.058 mol) in DMSO (100 mL) at ambient temperature was added ethyl 4-amino-piperidinecarboxylate (10 g., 0.058 mol). After 10 min, α-(p-toluenesulfonyl)-4-

fluorobenzylisocyanide (8.4 g, 0.029 mol) and K_2CO_3 (8.0 g, 0.058 mol) were added. After stirring for 18 h, the solution was partitioned between EtOAc and 3 N HCl and the organic phase was washed with 3N HCl. The combined aqueous layers were neutralized with solid K_2CO_3 and extracted twice with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil which solidified upon standing. Flash chromatography eluting consecutively with 33%, 50% and 67% EtOAc in hexanes followed by trituration with ether afforded the title compound as a white solid; yield 3.5 g (23%).

b) 1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(3-N,N-dimethylamino-*trans*-1-propenone)imidazole A mixture of 1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole (16 g, 0.044 mol) and DMFDMA (30 mL) was heated to 100 °C for 18 h. Excess DMFDMA was removed *in vacuo* and the residue was filtered through a pad of silica gel eluting with 4% MeOH in CH_2Cl_2 to afford the title compound as a yellow foam; yield 18 g (99%): 1H NMR ($CDCl_3$) δ 7.65 (1H, s), 7.55 (2H, m), 7.48 (1H, m), 7.02 (2H, t, $J = 8.7$ Hz), 5.02 (1H, d, $J = 12.6$ Hz), 4.91 (1H, m), 4.30 (2H, m), 4.13 (2H, q, $J = 7.1$ Hz), 2.99 (3H, br s), 2.89 (2H, m), 2.51 (3H, br s), 2.18 (2H, d, $J = 12.1$ Hz), 1.78 (2H, dq, $J = 4.3, 12.3$ Hz), 1.26 (3H, t, $J = 7.1$ Hz).

c) 4-(4-Fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-[(1-ethoxycarbonyl)piperidin-4-yl]imidazole
To a solution of 1-(1-ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(3-N,N-dimethylamino-*trans*-1-propenone)imidazole (15 g, 0.36 mol) in DMSO was added phenylguanidine (13 g, 0.094 mol). The reaction mixture was heated to 150 °C for 24 h, cooled to ambient temperature and poured into H_2O . The resulting precipitate was collected, washed with H_2O and air-dried. Vacuum filtration through a pad of silica gel eluting with 2% MeOH in CH_2Cl_2 followed by trituration with ether afforded the title compound as an off-white solid; yield 14 g (80%):

4-(4-Fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole A solution of 4-(4-fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-[(1-ethoxycarbonyl)piperidin-4-yl]imidazole (12 g) in conc HCl was heated to reflux for 18 h. After cooling to ambient temperature, the reaction mixture was neutralized with solid Na_2CO_3 and the resulting precipitate was collected and air-dried. Flash chromatography

eluting consecutively with 90/10/1 and 80/20/2 CH₂Cl₂ followed by recrystallization from CH₂Cl₂/EtOAc afforded 5.2 g of the title compound.

Example 21

5 4-(4-Fluorophenyl)-5-[(2-[t-butyloxycarbonylamino]ethylamino)pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperidin-4-yl]imidazole

A solution of 5-(2-methylsulfinyl-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-t-butoxycarbonyl)-4-piperidinyl]imidazole (0.30 g, 0.62 mmol) and N-t-butyloxycarbonyl-1,2-ethylenediamine [Krapcho, P. A.; Kuell, C. S. *Syn. Commun.* 1990, 20(16),
10 2559, (0.18 g, 0.67 mmol)] in DMF (20 mL) was heated for 18 h at 88 °C. The reaction mixture was cooled to ambient temperature, poured into H₂O and extracted with EtOAc. The organic extract was concentrated in vacuo and the residue was recrystallized from EtOAc/hexanes to afford the title compound as a light yellow solid; yield 0.28 g (77%); mp = 161-163 °C.

15

Example 22

4-(4-Fluorophenyl)-5-[(2-aminoethyl)amino]pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole

To a solution of 4-(4-Fluorophenyl)-5-[(2-[t-butyloxycarbonylamino]ethylamino)-pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperidin-4-yl]imidazole (0.20 g, 0.34 mmol) in
20 CH₂Cl₂ (15 mL) at ambient temperature was added TFA (99%, 20 mL). After stirring at ambient temperature for 2h, the volatiles were removed *in vacuo* and the residue dissolved in H₂O, neutralized with 10% aq NaOH and extracted with EtOAc. The solvent was removed *in vacuo* to afford the title compound as a white solid; yield 0.060 g (46%); mp = 125-126 °C.

25

Example 23

4-(4-Fluorophenyl)-5-[(2-(3-ethoxypropylamino)]pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperidin-4-yl]imidazole

Following the procedure of Example 21 except substituting 3-ethoxypropylamine for N-t-butyloxycarbonyl-1,2-ethylenediamine afforded the title compound as a white solid in
30 79% yield: mp = 102-103 °C.

Example 24

4-(4-Fluorophenyl)-5-[(2-ethoxypropyl)amino]pyrimidin-4-yl]-1-(piperdin-4-yl)imidazole

- 5 Following the procedure of Example 22 except substituting 4-(4-fluorophenyl)-5-[(2-(3-ethoxypropylamino))pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperdin-4-yl]imidazole for 4-(4-Fluorophenyl)-5-[(2-[t-butyloxycarbonylamino)-ethylamino]pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperdin-4-yl]imidazole afforded the title compound as a white solid in 68% yield: mp = 160-163 °C.

10

Example 25

4-(4-Fluorophenyl)-5-[2-[3-[imidazol-1-yl]propyl]aminopyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperdin-4-yl]imidazole

- 15 Following the procedure of Example 21 except substituting 1-(3-aminopropyl)-imidazole for N-t-butyloxycarbonyl-1,2-ethylenediamine afforded the title compound as a white solid in 69% yield: mp = 180-183 °C.

Example 26

4-(4-Fluorophenyl)-5-[2-[3-[imidazol-1-yl]propyl]aminopyrimidin-4-yl]-1-(piperdin-4-yl)imidazole

- 20 Following the procedure of Example 22 except substituting 4-(4-fluorophenyl)-5-[2-[3-[imidazol-1-yl]propyl]aminopyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperdin-4-yl]imidazole for 4-(4-Fluorophenyl)-5-[(2-[t-butyloxycarbonylamino)-ethylamino]-pyrimidin-4-yl)-1-[(1-t-butoxycarbonyl)piperdin-4-yl]imidazole afforded the title
25 compound as a white solid in 54% yield: mp = 90-92 °C.

Example 27

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-anilino-4-pyridinyl)imidazole

a) 2-Chloro-4-pyridinemethanol

- 30 To a suspension of NaBH₄ (4.66 g 123 mmol) in THF (400 mL) at 0 °C was added 2-chloro-4-pyridinedicarboxylic acid (12.9 g, 82.1 mmol) portionwise. The reaction

mixture was allow to warm to ambient temperature and stirred 1.5 h. $\text{BF}_3\text{O}(\text{Et})_2$ (19.2 mL, 156 mmol) in THF (125 mL) was added over 3 h and stirred at ambient temperature for 20 h, cooled to 0°C and 1.5 N HCl (100 mL) was added dropwise. The reaction mixture was allow to warm to ambient temperature, the solvent was evaporated under reduced pressure and 4 N NaOH solution was added to adjust the pH to 10-11. The solution was extracted three times with EtOAc and the combined organic layers were washed with brine, dried (MgSO_4), filtered, and the filtrate concentrated under reduced pressure to give the title compound as a white solid; yield 10.8 g (92%): ^1H NMR (CDCl_3) δ 8.30 (d, 1H, $J = 4.9$ Hz), 7.37 (s, 1H), 7.22 (d, 1H, $J = 4.9$ Hz), 4.76 (s, 2H), 2.50 (br-s, 1H).

b) 2-Chloro-4-pyridinecarboxaldehyde

A suspension of 2-chloro-4-pyridinemethanol (8.0 g, 55.9 mmol), NBS (14.9 g, 83.9 mmol), and K_2CO_3 (11.75 g, 97.1 mmol) in EtOAc was refluxed for 3 h. A second portion of NBS (14.9 g, 83.9 mmol) and Na_2CO_3 (12.0 g, 114 mmol) were added and the reaction was heated to reflux for an additional 3.5 h, cooled and filtered through a pad of celite. The filtrate, after concentration to a small volume, was subjected to flash chromatography eluting with 0.5-4% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$. The fractions containing product were combined, washed successively with sat aq NaHCO_3 , 10% $\text{Na}_2\text{S}_2\text{O}_3$, and brine, dried (MgSO_4) and concentrated *in vacuo* to give the title compound as a light yellow solid; yield 5.3 g (67%). ^1H NMR (CDCl_3) δ 10.06 (s, 1H), 8.66 (d, 1H, $J = 5.0$ Hz), 7.76 (s, 1H), 7.66 (d, 1H, $J = 5.0$ Hz).

c) 2-Chloro-4-pyridinecarboxaldehyde(1-t-butoxycarbonyl-4-aminopiperidine)imine

Following the procedure of Example 19b except substituting 2-chloro-4-pyridinecarboxaldehyde for 2-methylthiopyrimidine-4-carboxaldehyde afforded the title compound. ^1H NMR (CDCl_3) δ 8.45 (d, 1H, $J = 5.1$ Hz), 8.29 (s, 1H), 7.65 (s, 1H), 7.52 (d, 1H, $J = 5.1$ Hz), 4.05 (br-s, 2H), 3.48 (m, 1H), 3.03 (m, 2H), 1.73 (m, 4H), 1.48 (s, 9H).

d) 1-(1-t-Butoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-chloro-4-pyridinyl)imidazole

Following the procedure of Example 18d except substituting 2-chloro-4-pyridinecarboxaldehyde(1-t-butoxycarbonyl-4-aminopiperidine)imine for 2-

methylthiopyrimidine-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine afforded the title compound which after purification by flash chromatography eluting with 0-5% CH₃OH/CH₂Cl₂ followed by recrystallization from EtOAc/hexanes to gave a light yellow solid; 10.2 (60%): ESMS m/z = 457 (M^+ + H).

5 e) 1-(1-t-Butoxycarbonyl-4-piperidiny)-4-(4-fluorophenyl)-5-(2-anilino-4-pyridinyl)imidazole

To a suspension of NaH (130 mg, 3.3 mmol) in DMA (2 mL) was added aniline (0.58 mL, 6.1 mmol) and stirred until bubbling ceased. To this solution was added 1-(1-t-butoxycarbonyl-4-piperidiny)-4-(4fluorophenyl)-5-(2-chloro-4-pyridinyl)imidazole
10 (0.30 g, 0.66 mmol) and the resulting solution was heated at 120 °C until no evidence of starting material was observed by mass spectroscopy (1-3 days). To the cooled reaction mixture 1M NaOH was added and the resulting mixture extracted three times with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), filtered, and the filtrate concentrated under reduced pressure to afford a yellow residue which was
15 chromatographed with 50-80% EtOAc/hexanes. The resulting solid was triturated with Et₂O to give the title compound as a light yellow solid; yield 180 mg (53%): ESMS m/z = 514 (M^+ + H).

f) 1-(4-Piperidiny)-4-(4-fluorophenyl)-5-(2-anilino-4-pyridinyl)imidazole

To 1-(1-t-butoxycarbonyl-4-piperidiny)-4-(4-fluorophenyl)-5-(2-anilino-4-pyridinyl)imidazole (175 mg, 0.34 mmol) was added a cooled solution of TFA (12 mL)
20 at -10 °C. The reaction mixture was allowed to warm to ambient temperature and stirred at this temperature for 0.5 h. The solvent was evaporated under reduced pressure and the residue was dissolved in H₂O (10 mL) to which 3 N HCl (0.5 mL) was added. The acidic solution was extracted twice with EtOAc and made basic with 50% NaOH and
25 extracted three times with EtOAc. The combined organic extracts were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a white solid; 0.70 g (50%): ESMS m/z = 414 (M^+ + H)

Example 28

30 trans-5-[2-(Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-hydroxycyclohexyl)imidazole

To a solution of the ketone (0.325 mg., 0.76 mmol.) produced in accordance with Example 17 above, in THF/MeOH (4 mL) was added NaBH₄ (0.1g) in MeOH (2.5mL) and the mixture was stirred for 1h. The reaction mixture was quenched with Sat. Na₂CO₃ and the product was extracted with EtOAc. Evaporation of the extract and crystallization from CH₂Cl₂/ Me₂CO afforded the title compound. mp 204 - 206 °C.

By methods analogous to those described above for Examples 2 to 28 the following additional compounds may be synthesized:

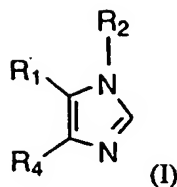
- 10 4-(4-Fluorophenyl)-5-[(2-(3-chlorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
4-(4-Fluorophenyl)-5-[(2-(3-fluorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
4-(4-Fluorophenyl)-5-[(2-(3-trifluoromethylphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
15 4-(4-Fluorophenyl)-5-[(2-(3-benzyloxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
4-(4-Fluorophenyl)-5-[(2-(3-hydroxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
20 4-(4-Fluorophenyl)-5-[(2-(4-chlorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
4-(4-Fluorophenyl)-5-[(2-(4-fluorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
4-(4-Fluorophenyl)-5-[(2-(4-trifluoromethylphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
25 4-(4-Fluorophenyl)-5-[(2-(4-benzyloxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
4-(4-Fluorophenyl)-5-[(2-(4-hydroxyphenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole
30 4-(4-Fluorophenyl)-5-[(2-(3,4-dichlorophenyl)amino)pyrimidin-4-yl]-1-(piperidin-4-yl)imidazole

4-(4-Fluorophenyl)-5-[(2-(3,4-difluorophenyl)amino)pyrimidin-4-yl]-1-(piperdin-4-yl)imidazole

- 5 The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be
- 10 construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A compound of the formula :



wherein

- 5 R_1 is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is substituted with NHR_a and optionally with an additional independent substituent selected from C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12} , amino, mono and di- C_{1-6} alkyl substituted amino, $o\ N(R_{10})C(O)R_b$ or NHR_a ;
- 10 R_a is aryl, aryl C_{1-6} alkyl, heterocyclic, heterocyclyl C_{1-6} alkyl, heteroaryl, heteroaryl C_{1-6} alkyl, wherein each of these moieties may be optionally;
- R_b is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclyl, or heterocyclyl C_{1-4} alkyl;
- R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted
- 15 by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{16}$, $-(CR_{10}R_{20})_vCOR_{12}$, $-SR_5$, $-SOR_5$, $-OR_{12}$, halo-substituted- C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{12}$, $-NR_{10}C(Z)R_{16}$, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen,
- 20 cyano, $-C(Z)NR_{13}R_{14}$, $-C(Z)OR_3$, $-(CR_{10}R_{20})_mCOR_3$, $-S(O)_mR_3$, $-OR_3$, halo-substituted- C_{1-4} alkyl, C_{1-4} alkyl, $-(CR_{10}R_{20})_mNR_{10}C(Z)R_3$, $-NR_{10}S(O)_mR_8$, $-NR_{10}S(O)_mNR_7R_{17}$, $-ZC(Z)R_3$ or $-(CR_{10}R_{20})_mNR_{13}R_{14}$;
- v is 0, or an integer having a value of 1 or 2;
- m is 0, or the integer 1 or 2;
- 25 m' is an integer having a value of 1 or 2,
- m'' is 0, or an integer having a value of 1 to 5;
- R_2 is C_{1-10} alkyl N_3 , $-(CR_{10}R_{20})_nOR_9$, heterocyclyl, heterocyclyl C_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7}

- cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀ alkyl, C₅₋₇ cycloalkenyl,
 C₅₋₇cycloalkenyl-C₁₋₁₀-alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl,
 heteroaryl-C₁₋₁₀-alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈,
 (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄, (CR₁₀R₂₀)_nNO₂,
 5 (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nSO₂R₁₈, (CR₁₀R₂₀)_nS(O)_mNR₁₃R₁₄,
 (CR₁₀R₂₀)_nC(Z)R₁₁, (CR₁₀R₂₀)_nOC(Z)R₁₁, (CR₁₀R₂₀)_nC(Z)OR₁₁,
 (CR₁₀R₂₀)_nC(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nC(Z)NR₁₁OR₉,
 (CR₁₀R₂₀)_nNR₁₀C(Z)R₁₁, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄,
 (CR₁₀R₂₀)_nN(OR₆)C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nN(OR₆)C(Z)R₁₁,
 10 (CR₁₀R₂₀)_nC(=NOR₆)R₁₁, (CR₁₀R₂₀)_nNR₁₀C(=NR₁₉)NR₁₃R₁₄,
 (CR₁₀R₂₀)_nOC(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄,
 (CR₁₀R₂₀)_nNR₁₀C(Z)OR₁₀, 5-(R₁₈)-1,2,4-oxadiazol-3-yl or
 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl,
 heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be
 15 optionally substituted;
- n is an integer having a value of 1 to 10;
 n' is 0, or an integer having a value of 1 to 10;
 Z is oxygen or sulfur;
 R₃ is heterocyclyl, heterocyclylC₁₋₁₀ alkyl or R₈;
- 20 R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the
 moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being -SOH;
- R₆ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl,
 arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclic, aroyl, or C₁₋₁₀
 alkanoyl;
- 25 R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇
 together with the nitrogen to which they are attached form a heterocyclic ring of 5 to
 7 members which ring optionally contains an additional heteroatom selected from
 oxygen, sulfur or NR₁₅;
- 30 R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇
 cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀
 alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈.

- (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
- R₉ is hydrogen, -C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;
- 5 R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;
- R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl;
- R₁₂ is hydrogen or R₁₆;
- R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋
- 10 4 alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉ ;
- R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;
- 15 R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;
- R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroarylalkyl;
- R₁₉ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl; or a pharmaceutically acceptable salt thereof.
- 20
2. The compound according to Claim 1 wherein R₁ is a substituted 4-pyridyl or 4-pyrimindyl.
3. The compound according to Claim 1 wherein R_a is substituted one or more times,
- 25 independently, by halogen; C₁₋₄; halo-substituted alkyl; hydroxy; hydroxy substituted C₁₋₄ alkyl; C₁₋₄ alkoxy; S(O)_malkyl and S(O)_m aryl (wherein m is 0, 1, or 2); C(O)OR₁₁; C(O)R₁₁; OC(O)R₁₈; O-(CH₂)_s-O and s is an integer of 1 to 3; amino; mono- and di-C₁₋₆ alkylsubstituted amino; N(R₁₀)C(O)R_b; an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom
- 30 selected from oxygen, sulfur or NR₁₅; optionally substituted aryl; or an optionally substituted aryl C₁₋₄ alkyl.

4. The compound according to Claim 3 wherein R_a is aryl, arylalkyl,
halosubstituted arylalkyl, halosubstituted aryl, heterocyclic alkyl, hydroxy alkyl, alkyl-1-
piperidine-carboxylate, heterocyclic, alkyl substituted heterocyclic, halosubstituted
5 heterocyclic, or aryl substituted heterocyclic.
5. The compound according to Claim 3 wherein R_a is benzyl, halosubstituted
benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, morpholinopropyl, ethyl-1-
piperidinecarboxylate, piperonyl, piperidin-4-yl, alkyl substituted piperidine,
10 chlorotryptamine, and tetrathiohydropyranyl.
6. The compound according to any of Claims 1 to 5 wherein R_4 is an optionally
substituted phenyl.
- 15 7. The compound according to Claim 6 wherein the phenyl is substituted one or
more times independently by halogen, $-SR_5$, $-S(O)R_5$, $-OR_{12}$, halo-substituted- C_{1-4}
alkyl, or C_{1-4} alkyl.
8. The compound according to any of Claims 1 to 6 wherein R_2 is selected from
optionally substituted heterocyclcyl, optionally substituted heterocyclcyl C_{1-10} alkyl,
20 $(CR_{10}R_{20})_nNS(O)_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, aryl C_{1-10} alkyl,
 $(CR_{10}R_{20})_nNR_{13}R_{14}$, optionally substituted C_{3-7} cycloalkyl, or optionally substituted
 C_{3-7} cycloalkyl C_{1-10} alkyl.
9. The compound according to Claim 8 wherein R_2 is morpholino propyl,
25 piperidine, N-methylpiperidine, N-benzylpiperidine, 2,2,6,6-tetramethylpiperidine, 4-
aminopiperidine, 4-amino-2,2,6,6-tetramethyl piperidine, 4-hydroxycyclohexyl,
4-methyl-4-hydroxy cyclohexyl, 4-pyrrolinindyl-cyclohexyl, 4-methyl-4-
aminocyclohexyl, 4-methyl-4-acetamidocyclohexyl, 4-keto cyclohexyl, 4-oxiranyl, or 4-
hydroxy-4-(1-propynyl)cyclohexyl.
30
10. The compound according to Claim 1 which is:

- 5-[(2-Benzylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-[2-(4-tetrahydrothiopyranyl)aminopyrimidin-4-yl]imidazole
- 5 4-(4-Fluorophenyl)-5-[(2-hydroxy)ethylamino]pyrimidin-4-yl-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(3-Chlorobenzylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 10 5-[(2-(1-Naphthylmethylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(1-Benzyl-4-piperidinylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-[2-[3-(morpholino)propyl]aminopyrimidin-4-yl]imidazole
- 15 5-[2[(3-Bromophenyl)amino]pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2(Piperonylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(4-Piperidinylamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 20 5-[(2-(5-Chlorotryptamino)pyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[(2-(2,2,6,6-tetramethylpiperidin-4-yl)aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 25 5-[(2-[(1-Ethoxycarbonyl)piperdin-4-yl]aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole
- 5-[2-(Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-oxocyclohexyl)imidazole
- 5-[4-(2-Phenylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-hydroxycyclohexyl)imidazole
- 30 4-(4-Fluorophenyl)-1-(1-methylpiperdin-4-yl)-5-(2-phenylamino)pyrimidin-4-yl)imidazole

4-(-Fluorophenyl)-1-(2,2,6,6-tetramethylpiperdin-4-yl) 5-[(2-phenylamino)-pyrimidin-4-yl]imidazole

4-(4-Fluorophenyl)-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperdin-4-yl)imidazole

4-(4-Fluorophenyl)-5-[2-[3-[imidazol-1-yl)propyl]aminopyrimidin-4-yl]-1-[(1-t-

5 butoxycarbonyl)piperdin-4-yl]imidazole

4-(4-Fluorophenyl)-5-[2-[3-[imidazol-1-yl)propyl]aminopyrimidin-4-yl]-1-(piperdin-4-yl)imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-anilino-4-pyridinyl)imidazole

or a pharmaceutically acceptable salt thereof.

10

11. A pharmaceutical composition comprising a compound according to any of Claims 1 to 10 and a pharmaceutically acceptable carrier or diluent.

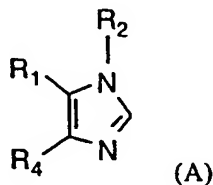
12. A method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in
15 need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to Claim 1.

13. The method according to claim 12 wherein the mammal is afflicted with a
CSBP/RK/p38 kinase mediated disease selected from rheumatoid arthritis, rheumatoid
20 spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, Crohn's disease, ulcerative
25 colitis, inflammatory bowel disease, neurotrauma, CNS injury, restinosis, reprefusion injury, psoriasis, or pyresis.

14. A method of treating inflammation in a mammal in need thereof, which
comprises administering to said mammal an effective amount of a compound of Formula
30 (I) according to any of Claims 1 to 10.

15. A method of treating osteoporosis in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to any of Claims 1 to 10.

5 16. A compound of the formula:



wherein

R₁ is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is substituted with NHR_a and optionally with an additional independent substituent selected from C₁₋₄ alkyl, halogen, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di-C₁₋₆ alkyl substituted amino, N(R₁₀)C(O)R_b or NHR_a;

R_a is C₁₋₆alkyl substituted one or more times, independently by halogen; hydroxy; C₁₋₁₀; S(O)_m alkyl, wherein m is 0, 1 or 2; amino, mono & di-C₁₋₄ alkyl substituted amino; C₃₋₇ cycloalkyl; C₃₋₇ cycloalkyloxy; or a moiety having the formula A₁-B₁-D₁ :

wherein A₁ is CR₁₀R₂₀, oxygen, sulfur, or NR₁₀R₂₀;

B₁ is C(O) or S(O)₂;

D₁ is E₁ or E₂ ; E₁ is C₁₋₁₀ alkyl, aryl, aryl C₁₋₆ alkyl, heteroaryl, heteroaryl C₂₋₆ alkenyl, heterocyclic, or heterocyclic C₁₋₆ alkyl; and E₂ is O-E₁ or N-E₁;

R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl;

R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, -C(Z)NR₇R₁₇, -C(Z)OR₁₆, -(CR₁₀R₂₀)_vCOR₁₂, -SR₅, -SOR₅, OR₁₂, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₁₂, -NR₁₀C(Z)R₁₆, or (CR₁₀R₂₀)_vNR₁₀R₂₀ and which, for other positions of substitution, is halogen,

- cyano, $-C(Z)NR_{13}R_{14}$, $-C(Z)OR_3$, $-(CR_{10}R_{20})_mCOR_3$, $-S(O)_mR_3$, $-OR_3$, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, $-(CR_{10}R_{20})_mNR_{10}C(Z)R_3$, $-NR_{10}S(O)_mR_8$, $-NR_{10}S(O)_mNR_7R_{17}$, $-ZC(Z)R_3$ or $-(CR_{10}R_{20})_mNR_{13}R_{14}$;
- v is 0, or an integer having a value of 1 or 2;
- 5 m is 0, or the integer 1 or 2;
- m' is an integer having a value of 1 or 2,
- m" is 0, or an integer having a value of 1 to 5;
- R₂ is $-(CR_{10}R_{20})_nOR_9$, heterocyclyl, heterocyclylC₁₋₁₀ alkyl, C₁₋₁₀alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl,
- 10 C₃₋₇cycloalkylC₁₋₁₀ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇ cycloalkenyl C₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nSO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mNR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$,
- 15 $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$,
- 20 $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-(R₁₈)-1,2,4-oxadiazol-3-yl or 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cycloalkyl, cycloalkyl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;
- n is an integer having a value of 1 to 10;
- 25 n' is 0, or an integer having a value of 1 to 10;
- Z is oxygen or sulfur;
- R₃ is heterocyclyl, heterocyclylC₁₋₁₀ alkyl or R₈;
- R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being -SOH;
- 30 R₆ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroaryl₁₋₄alkyl, heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;

- R7 and R17 is each independently selected from hydrogen or C₁₋₄ alkyl or R7 and R17 together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;
- 5 R8 is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
- 10 R9 is hydrogen, -C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;
- R10 and R20 is each independently selected from hydrogen or C₁₋₄ alkyl;
- R11 is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl;
- 15 R12 is hydrogen or R16;
- R13 and R14 is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from
- 20 oxygen, sulfur or NR₉ ;
- R15 is R10 or C(Z)-C₁₋₄ alkyl;
- R16 is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;
- R18 is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, aryl₁₋₁₀alkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroaryl₁₋₁₀alkyl;
- 25 R19 is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;
- or a pharmaceutically acceptable salt thereof.
17. The compound according to Claim 16 wherein R₁ is a 4-pyridyl or 4-pyrimidine ring, and R₄ is an optionally substituted phenyl.

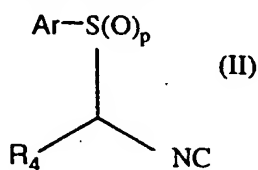
30

18. The compound according to Claim 16 or 17 wherein R₂ is selected from optionally substituted heterocyclyl, optionally substituted heterocyclylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nNS(O)₂R₁₈, (CR₁₀R₂₀)_nS(O)_mR₁₈, arylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nNR₁₃R₁₄, optionally substituted C₃₋₇cycloalkyl, or optionally substituted C₃₋₇cycloalkyl C₁₋₁₀ alkyl.
19. The compound according to Claim 16 which is:
4-(4-Fluorophenyl)-5-[(2-hydroxy)ethylamino]pyrimidin-4-yl-1-(1-methyl-piperdin-4-yl)imidazole
4-(4-Fluorophenyl)-5-[2-(2-hydroxy)ethylaminopyrimidin-4-yl]-1-(2,2,6,6-tetramethylpiperdin-4-yl)-imidazole
4-(4-Fluorophenyl)-5-[(2-(3-ethoxypropylamino))]pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperdin-4-yl]imidazole
4-(4-Fluorophenyl)-5-[(2-[t-butyloxycarbonylamino)ethylamino]pyrimidin-4-yl]-1-[(1-t-butoxycarbonyl)piperdin-4-yl]imidazole
4-(4-Fluorophenyl)-5-[(2-aminoethyl)amino]pyrimidin-4-yl]-1-(piperdin-4-yl)-imidazole
4-(4-Fluorophenyl)-5-[(2-ethoxypropyl)amino]pyrimidin-4-yl]-1-(piperdin-4-yl)-imidazole; or a pharmaceutically acceptable salt thereof.
20. A pharmaceutical composition comprising a compound according to Claim 16, and a pharmaceutically acceptable carrier or diluent.
21. A method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (A) according to Claim 16.
22. The method according to claim 21 wherein the mammal is afflicted with a CSBP/RK/p38 kinase mediated disease selected from rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory

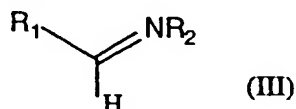
disease, silicosis, pulmonary sarcososis, bone resorption diseases, osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, Crohn's disease, ulcerative colitis, inflammatory bowel disease, neurotrauma, CNS injury, restinosis, reprefusion injury, psoriasis, or pyresis.

5

23. A process for preparing a compound of Formula (I), or Formula (A) as defined in Claim 1 or 16 which comprises reacting a compound of the Formula (II) :



with a compound of the Formula (III):



10

wherein p is 0 or 2; and a base strong enough to deprotonate the isonitrile moiety of Formula (II); and R₁, R₂ and R₄ are as defined in Claim 1 or are precursors of the groups R₁, R₂ and R₄ and Ar is an optionally substituted phenyl group, and thereafter if necessary, converting a precursor of R₁, R₂ and R₄ to a group R₁, R₂ and R₄.

15

24. The process according to Claim 23 wherein the reaction, when p=0, utilizes TBD as a base.

25. The process according to Claim 23 wherein the reaction, when p=2, the base is an amine, a carbonate, a hydride, or an alkyl or aryl lithium reagent.

20

26. The process according to Claim 23 wherein the imine of Formula (III), is isolated prior to reaction with Formula (II).

27. The process according to Claim 23 wherein the imine of Formula (III), is formed in situ prior to reaction with Formula (II).

25

28. The process according to Claim 27 wherein the imine is formed in situ by reacting an aldehyde of the formula $R_4\text{CHO}$, wherein R_4 is as defined for Formula (I), with a primary amine of the formula $R_2\text{NH}_2$, wherein R_2 is as defined for Formula (I).

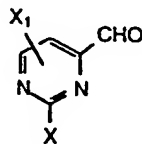
5

29. The process according to Claim 27 wherein formation of the imine in situ utilizes dehydrating conditions.

30. The process according to Claim 28 wherein the solvent is N,N-dimethylformamide (DMF), halogenated solvents, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, benzene, or toluene, or DME.

10

31. The process according to Claim 28 wherein the aldehyde $R_4\text{CHO}$ is a pyrimidine aldehyde of the formula:



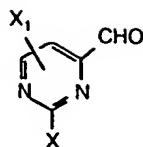
15

wherein X is NHR_a and X_1 is defined as the optional substituent group on the R_1 moiety in Formula (I), or Formula (A) according to Claim 1 or 16, to yield a compound of Formula (I), or (A) or a pharmaceutically acceptable salt thereof.

20 32. The process according to Claim 28 wherein the primary amine $R_2\text{NH}_2$ is a heterocyclyl amine, heterocyclyl C_{1-10} alkyl amine, C_{3-7} cycloalkyl amine, C_{3-7} cycloalkyl C_{1-10} alkyl amine, all of which may be optionally substituted.

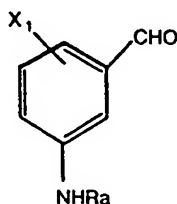
25 33. The process according to Claim 32 wherein R_2 moiety of the $R_2\text{NH}_2$ group is morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, 2,2,6,6-tetramethylpiperidine, 4-aminopiperidine, 4-amino-2,2,6,6-tetramethyl piperidine, 4-hydroxycyclohexyl, 4-methyl-4-hydroxy cyclohexyl, 4-pyrrolinindyl-cyclohexyl, 4-methyl-4-aminocyclohexyl, 4-methyl-4-acetamidocyclohexyl, 4-keto cyclohexyl, 4-oxiranyl, or 4-hydroxy-4-(1-propynyl)cyclohexyl.

34. A compound of the formula:

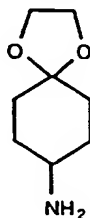


wherein X is NHR_a and X_1 is defined as the optional substituent group on the R_1 moiety
 5 in Formula (I), or Formula (A) according to Claim 1 or 16.

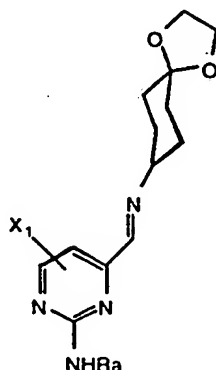
35. A process for preparing a compound of Formula (I), or Formula (A) as defined in
 Claim 1 or 16 which comprises reacting a compound of the formula:



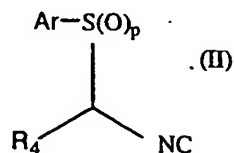
10 wherein X_1 is defined as the optional substituent group on the R_1 moiety in Formula (I),
 or Formula (A) with a compound of the formula:



to yield an intermediate of the formula:

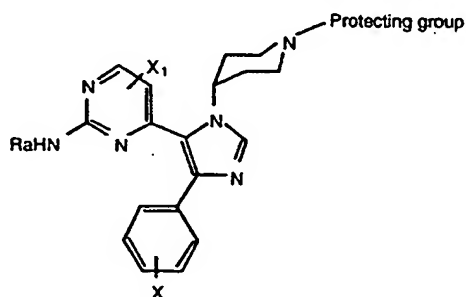


which is reacted with a compound of Formula (II) :



- wherein R_4 is as defined for Formula (I), p is 0 or 2, and the Ar ring is an optionally substituted phenyl, or R_1 , R_2 and R_4 are precursors of the groups R_1 , R_2 and R_4 as defined in Formula (I), and thereafter if necessary, converting a precursor of R_1 , R_2 and R_4 to a group R_1 , R_2 and R_4 , and converting the ketal to a desired substituted cycloalkyl moiety.

36. A process for preparing a compound of Formula (I), or Formula (A) as defined in Claim 1 or 16 which comprises reacting a compound of the formula



- wherein X_1 is an optional R_1 substituent as defined in Formula (I) or (A), and X is an optional substituent as defined for R_4 in Formula (I) or (A),
under suitable conditions to remove the protecting group and yield a compound of Formula (I) or (A) or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10039

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/505; C07D 403/04

US CL : 514/275; 544/331

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/275; 544/331

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,323,570 A (STENZEL ET AL.) 06 April 1982, column 1, lines 14-35.	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

24 JULY 1996

Date of mailing of the international search report

27 AUG 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

R.W. RAMSUER jd

Facsimile No. (703) 305-3230

Telephone No. (703) 308-1235